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United States
Environmental Protection
Agency

Evaluation of P-Listed Pharmaceutical Residues in Empty Pharmaceutical Containers

Prepared for:
U.S. Environmental Protection Agency
Office of Research and Development
Waste Management Branch,
National Risk Management Research Laboratory
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Notice

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Foreword

The US Environmental Protection Agency (US EPA) is charged by Congress with protecting the Nation's land, air, and water resources. Under a mandate of national environmental laws, the Agency strives to formulate and implement actions leading to a compatible balance between human activities and the ability of natural systems to support and nurture life. To meet this mandate, US EPA's research program is providing data and technical support for solving environmental problems today and building a science knowledge base necessary to manage our ecological resources wisely, understand how pollutants affect our health, and prevent or reduce environmental risks in the future.

The National Risk Management Research Laboratory (NRMRL) is the Agency's center for investigation of technological and management approaches for preventing and reducing risks from pollution that threaten human health and the environment. The focus of the Laboratory's research program is on methods and their cost-effectiveness for prevention and control of pollution to air, land, water, and subsurface resources; protection of water quality in public water systems; remediation of contaminated sites, sediments and ground water; prevention and control of indoor air pollution; and restoration of ecosystems. NRMRL collaborates with both public and private sector partners to foster technologies that reduce the cost of compliance and to anticipate emerging problems. NRMRL's research provides solutions to environmental problems by: developing and promoting technologies that protect and improve the environment; advancing scientific and engineering information to support regulatory and policy decisions; and providing the technical support and information transfer to ensure implementation of environmental regulations and strategies at the national, state, and community levels.

This publication has been produced as part of the Laboratory's strategic long-term research plan. It is published and made available by US EPA's Office of Research and Development to assist the user community and to link researchers with their clients.

Cynthia Sonich-Mullin, Director
National Risk Management Research Laboratory

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1 Abbreviations and Acronyms

DI	Deionized Water
DQO	Data Quality Objectives
EPA	Environmental Protection Agency
OSWER	Office of Solid Waste and Emergency Response
QAPP	Quality Assurance Project Plan
RCRA	Resource Conservation and Recovery Act
$T_{max\ wt\ loss}$	Temperature at which the peak in weight loss occurs for the residuals
TGA	Thermal Gravimetric Analysis

2 Executive Summary

Under the Resource Conservation and Recovery Act (RCRA), some discarded pharmaceuticals are considered acute hazardous wastes because their sole active pharmaceutical ingredients are P-listed commercial chemical products (40 CFR 261.33). Hospitals and other healthcare facilities have struggled with RCRA's empty container requirements when it comes to the disposal of visually empty warfarin and nicotine containers, and this issue is in need of investigation. For example, nicotine gums, patches and lozenges are hazardous wastes because nicotine and its salts are listed as P075, and Coumadin (also known as warfarin) is hazardous because warfarin and its salts are listed as P001 (when warfarin is present at concentrations greater than 0.3%).

Therefore, when unused nicotine-based smoking cessation products (e.g., patches, gums and lozenges) and Coumadin are discarded, they are classified as acute hazardous wastes, and must be managed in accordance with all applicable RCRA regulations. Furthermore, due to additional management requirements for P-listed wastes, any acute hazardous waste residues remaining in containers (and therefore the container itself) must be managed as hazardous unless the container has been rendered "RCRA empty" either by triple-rinsing with an appropriate solvent or by another method proven to achieve equivalent removal.

The primary objective of the current study was to answer the research question “Is there a difference between empty P-listed pharmaceutical containers that are triple-rinsed and those that are not triple-rinsed?” The study objective was accomplished via two tasks: 1) calculating the “maximum possible weight of residual drug/total residual /container” for each compound and packaging combination to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container and 2) evaluating, qualitatively, the presence of active pharmaceutical ingredient in the residues. The experimental test program included the use of a sensitive balance to determine the total amount of residues in the empty pharmaceutical containers and a thermal gravimetric analysis to qualitatively evaluate the presence of the active pharmaceutical compounds in the residues. The P-listed pharmaceuticals evaluated in the study were nicotine, Coumadin, and physostigmine.

The results of the study indicated the following: 1) all the medications in liquid form (Nicotrol nasal spray 10 mg/ml and Physostigmine salicylate 1 mg/ml) as well as the Nicotine inhaler (10mg/ cartridge) showed a difference between triple-rinsed containers and those that were not triple-rinsed because the residues in the not-triple-rinsed ones contained the active pharmaceutical ingredient; 2) the TGA results for the medications in solid form (i.e., tablet (caplet form), gum, and lozenge) and patches showed no difference between triple-rinsed containers and those that were not triple-rinsed. However, this conclusion is based on a qualitative analysis by thermal gravimetric analysis (TGA) that is limited by the sensitivity of the TGA. Other analytical techniques (e.g., gas chromatography or liquid chromatography equipped with mass spectrometer) may be needed to verify the TGA results for these medications, and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any); 3) the medications packaged in blister packs and plastic wraps contained minimal residuals, within the range of the error of the balance used in the study, after removing the drugs; 4) medications packaged in plastic containers contained measurable amount of residuals (using balance data) after removing the drugs (except for Nicorette 2 mg and 4 mg lozenges, for which the balance data were inconclusive); and 5) a theoretical “maximum possible weight of residual active compound/total residual /container” was calculated and presented for each compound and packaging combination.

3 Project Objective

The primary purpose of this study is to evaluate if simply removing the drug (specifically nicotine, Coumadin and physostigmine) from its container is equivalent to triple rinsing the container. The secondary purpose of this study was to determine whether the active pharmaceutical ingredient is present in the residues remaining in the containers. The U.S. Environmental Protection Agency (EPA) Office of Solid Waste and Emergency Response (OSWER) plans to address the issue of rendering these pharmaceutical packages RCRA empty through a rulemaking. The objectives of this study were achieved as follows:

- Measure the amount of total residuals in pharmaceutical containers containing warfarin, physostigmine and nicotine medications after removing the drugs.
- Calculate the "maximum possible weight of residual drug/total residual /container" for each compound and packaging combination. This calculated result may be used to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container.
- Use thermal gravimetric analysis (TGA) technique to qualitatively evaluate the presence of active pharmaceutical ingredient in the residuals after removing the drug from the rinsed pharmaceutical containers.

4 Approach

4.1 Experimental Approach

The investigated medications and package types are summarized in Table 1.

Table 1. List of medications and package types

Medication	Form and Dose	Package Type
Warfarin	Warfarin sodium tablets (caplet), 1 mg	Plastic container
	Warfarin sodium tablets (caplet), 5 mg	Plastic container
	Warfarin sodium tablets (caplet), 10 mg	Plastic container
	Warfarin sodium tablets (caplet), 2 mg	Blister pack
	Jantoven tablets (caplet), 1 mg	Blister pack
	Jantoven tablets (caplet), 10 mg	Blister pack
Nicotine	Nicorette gum, 2 mg	Blister pack
	Nicorette gum, 4 mg	Blister pack
	Nicotine polacrilex gum, 2 mg	Blister pack
	Nicotine polacrilex gum, 4 mg	Blister pack
	Nicorette mini lozenge, 2 mg	Plastic container
	Nicorette lozenge, 4 mg	Plastic container
	Nicotine transdermal patch, 7 mg	Plastic wrap (peel off) enclosed in foil wrap
	Nicotine transdermal patch, 14 mg	Plastic wrap (peel off) enclosed in foil wrap
	Nicotine transdermal patch, 21 mg	Plastic wrap (peel off) enclosed in foil wrap
	Nicotrol nasal spray, 10 mg/ml	Glass vial
	Nicotine inhaler, 10 mg/cartridge	Plastic container
Physostigmine Salicylate	Physostig-mine salicylate, 1 mg/ml	Glass ampule

Drugs were purchased from TriHealth outpatient pharmacy located in Cincinnati, OH. The drugs were purchased under a license issued from the Ohio Board of Pharmacy to the U.S. EPA. The license number is LR. 022271550.

The instruments utilized to determine the amount of residual drug and identify if these residuals contain the active pharmaceutical ingredient are:

1. Thermal Gravimetric Analysis (TGA) (model 2950, TA instruments)
2. Microbalance (AB104S-Mettler Toledo)

4.2 Experimental Steps

The medication (tablets, pills, lozenges, etc.) was removed from the container in a way to simulate actual use. The discarded medication was disposed as hazardous waste. For the Plastic Wrap peel offs, only the plastic peel was tested. The external foil wrap packaging was not tested because the active side of the nicotine patch is only in contact with the plastic wrap that is facing it, preventing the release of the drug to other surfaces. The drug can only release when the internal plastic wrap is peeled off. Therefore, the external foil package is not expected to contain residues as it is not in contact with the patch, and therefore it was not experimentally tested.

1. The empty containers were then exposed to one of three treatment conditions:

   A. No rinse
   B. Single triple rinse (30 seconds per rinse) with deionized water (DI)
   C. Double triple rinse (30 seconds per rinse) with organic solvent (methanol) to prepare clean containers (negative controls, because unused, empty containers could not be obtained)

2. Triplicate containers were evaluated under each one of the above three treatment conditions (Appendix A).

3. The amount of total residuals in each container was measured.

   A. Using a microbalance, the weight of the empty container was measured before and after treatment, and the difference in weight represented the amount of total residuals (i.e., the combined weights of the active pharmaceutical ingredient plus all the inactive ingredients). To dry the containers between triple-rinses, the container were kept upside down in a desiccator for a minimum of 12 hours.
   B. The balance readability is 0.1 mg

4. The maximum amount of active pharmaceutical ingredient that could theoretically be contained in the residuals of any of the tested medication was calculated as follows:

   A. It was assumed that the active pharmaceutical ingredient is homogenously distributed in the medication (e.g., tablet, lozenge, gum, etc.). This assumption represents the worst case scenario. Most likely, the outer layer of the medication is mainly composed of a different chemical coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body. In the case of liquid medications (solutions), the active pharmaceutical ingredient is homogeneously distributed in the residuals.
   B. Based on the above assumption, information on the concentration of the active pharmaceutical ingredient in the medication (e.g., % drug per tablet is calculated from the labeled drug concentration provided by the manufacturer), and the experimentally determined weight of total residuals, the maximum amount of active pharmaceutical ingredient that could theoretically be contained in the residuals was calculated. The detailed calculations for each medication/package are presented in Appendix A.

5. The TGA was used to qualitatively evaluate the presence of the active pharmaceutical compounds (warfarin sodium, nicotine, and physostigmine salicylate) in the residuals.

6. The residuals were collected from the empty containers after each treatment using a cotton tip applicator that was used to swab the container walls (Figure 1).

Figure 1. Cotton tip applicator and empty plastic containers

7. The cotton piece was then detached from the wooden stick and loaded into the TGA sample pan.

Figure 2. TGA Sample Pan

C. The weight loss of the cotton piece (loaded with residual, if any) as a function of temperature was measured using TGA (Figure 3). The TGA was programmed to heat the sample at a rate of 20 ºC/min to 600 ºC.
   a. The TGA balance readability is 0.1 µg

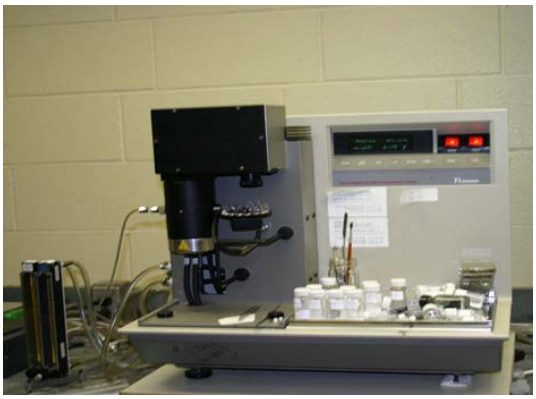


Figure 3. Thermogravimetric Analyzer (TGA)

D. The TGA is a technique in which the loss of mass of a substance is monitored as a function of temperature or time as the sample specimen is subjected to a controlled temperature program in a controlled atmosphere. The TGA instrument consists of a sample pan that is supported by a precision balance and a furnace (Figure 4). The sample pan containing the sample is heated to a specified temperature. The loss of the sample weight is monitored as a function of temperature. TGA relies on a high degree of precision in three measurements: weight, temperature, and temperature change. As a result of heating the sample to a high enough

temperature, some residuals decompose into gas, which disperses into the air. To prevent decomposition gases from entering the balance chamber, nitrogen gas was purged all the time at a rate of 100 ml/min. The TGA analysis generates a plot of % weight (Y-axis) and temperature (X-axis). The temperature at which the peak in weight loss ($T_{max\ wt\ loss}$) occurs for the collected residual from the empty drug container will be compared to that of the active pharmaceutical compound. If the $T_{max\ wt\ loss}$ for both the residual and the compounds are similar, then the residuals contain the active ingredient. It should be noted that the TGA data is qualitative, which means that the TGA results are not used to quantify the amount of active pharmaceutical ingredient in the residuals.

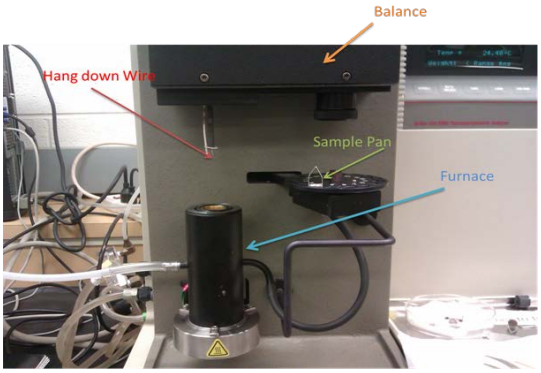


Figure 4. Components of the TGA instrument

E. The following controls were also analyzed in triplicates using the TGA:
   a. Clean cotton piece
   b. Negative control: clean empty containers cleaned with methanol
   c. Positive control: the active pharmaceutical compounds which are warfarin sodium, nicotine and physostigmine salicylate. The specifications of these compounds are presented in Table C2 (Appendix C).

5 Results and Discussion

5.1 Control Samples

5.1.1 Cotton Piece

The average $T_{max\ wt\ loss}$ of the cotton piece was 427 °C as presented by the first derivative of the profile of the weight loss as a function of temperature (Figure 5).

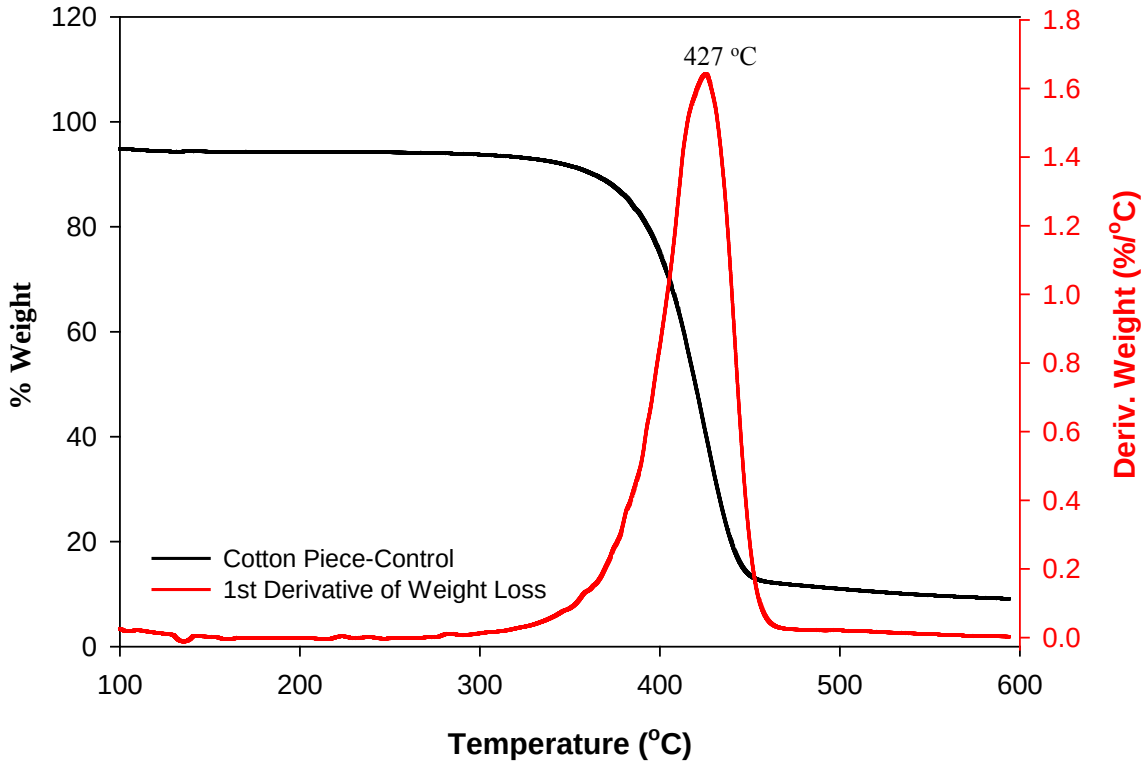


Figure 5. TGA results of cotton piece (control)

5.1.2 Warfarin Sodium Swabbed

The pure warfarin sodium had a distinct weight loss peak ($T_{max\ wt\ loss}$) at 313 °C in addition to the peak that corresponds to the weight loss of the cotton piece (Figure 6). According to the Quality Assurance Project Plan (QAPP) for this study, the $T_{max\ wt\ loss}$ of the residuals represents warfarin sodium if it occurs within ± 5 °C of the $T_{max\ wt\ loss}$ of the pure warfarin sodium (313 °C).

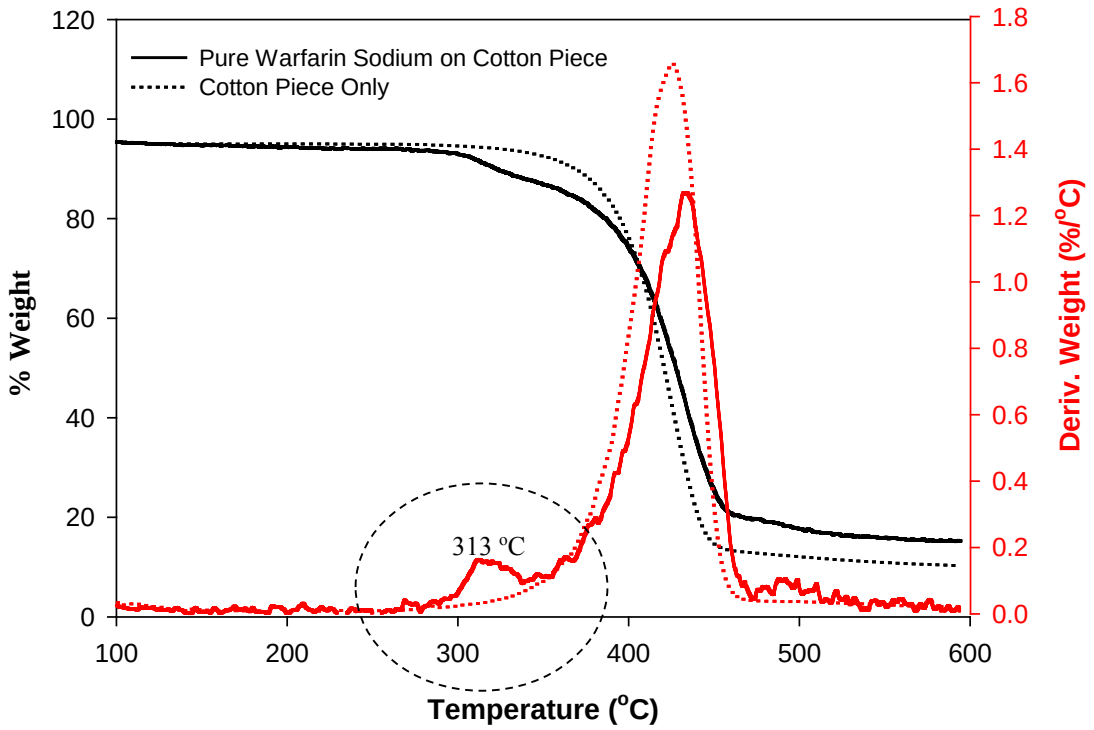


Figure 6. TGA results of Warfarin Sodium

It is noted that the weight loss profile and consequently its 1st derivative are somewhat noisy. The TGA analysis of the pure compounds (only warfarin and physostigmine) was performed after moving the TGA instrument inside a fume hood because of the very dangerous compounds that can emit from heating those compounds to elevated temperatures. Because the TGA balance is very sensitive, the air flow in the fume hood resulted in a somewhat noisy signal. Nonetheless, the overall profile was good and two distinct weight loss peaks were identified (one corresponds to the cotton piece and the other corresponds to the pure compound). Also, the $T_{max\ wt\ loss}$ of the cotton piece was within the acceptable limit for the cotton piece (Appendix C).

5.1.3 Nicotine Swabbed

The pure nicotine had a distinct weight loss peak at 217 °C in addition to the peak that corresponds to the weight loss of the cotton piece (Figure 7). According to the QAPP for this study, the $T_{max\ wt\ loss}$ of the residuals represents nicotine if it occurs within ± 5 °C of the $T_{max\ wt\ loss}$ of the pure nicotine (217 °C). It is noted that the weight loss profile and consequently its 1st derivative were NOT noisy because the pure nicotine analysis was conducted while the TGA was outside the fume hood so there was no air flow disturbance as happened for warfarin sodium and physostigmine salicylate.

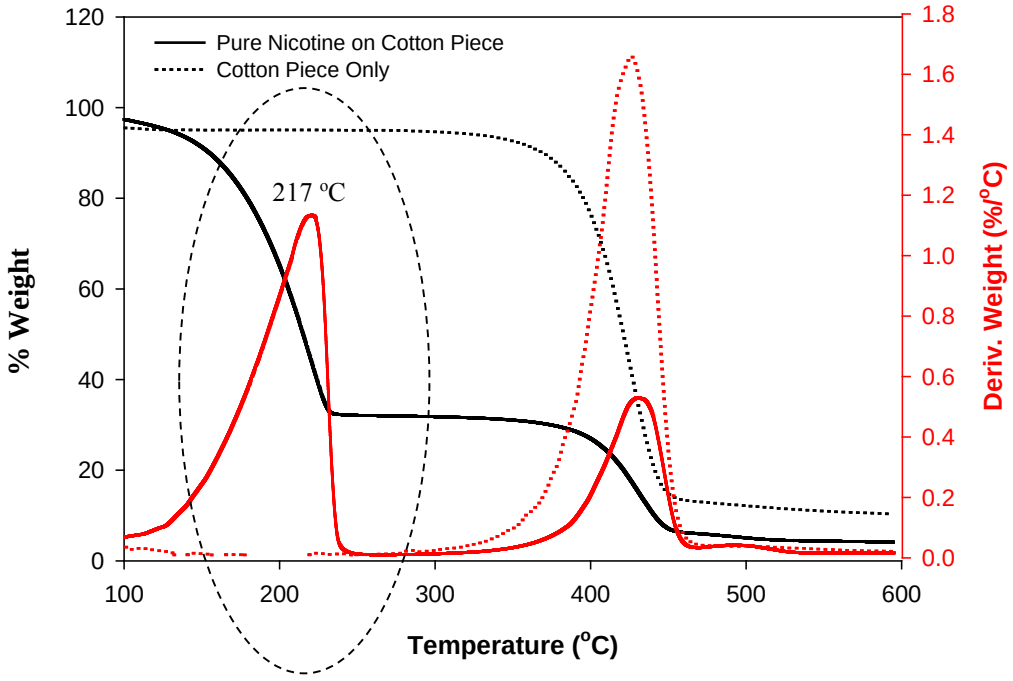


Figure 7. TGA results of pure Nicotine

5.1.4 Physostigmine Salicylate Swabbed

The pure physostigmine salicylate had a distinct weight loss peak at 236 °C in addition to the peak that corresponds to the weight loss of the cotton piece (Figure 8). According to the QAPP for this study, the $T_{max\ wt\ loss}$ of the residuals represents physostigmine if it occurs within ± 5 °C of the $T_{max\ wt\ loss}$ of the pure physostigmine (236 °C). It is noted that the weight loss profile and consequently its 1st derivative are somewhat noisy for the reasons stated in section 5.1.2.

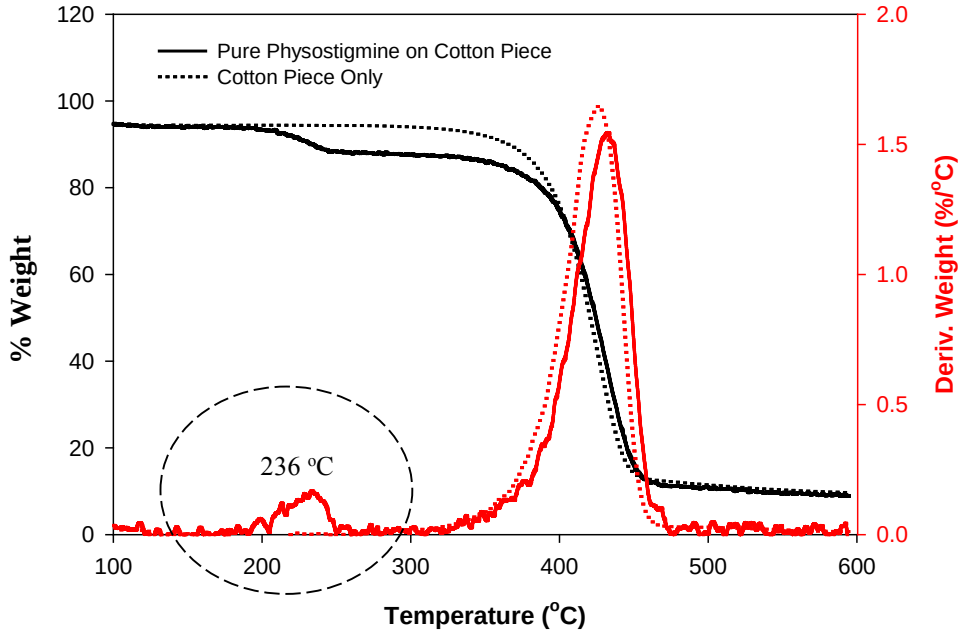


Figure 8. TGA results of pure Physostigmine Salicylate

5.2 Warfarin Sodium Medications

5.2.1 Warfarin Sodium Tablets, 1mg

Medication: Warfarin Sodium Tablets, 1 mg

Active compound: Warfarin Sodium

Manufacturer: Taro Pharmaceutical Industries Ltd

Form: Tablets

Package: Plastic Container

Lot#:124368

Expiration Date: 10/2015

Date Received: 03/25/2013

5.2.1.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 245 °C for the non-rinsed containers (Figure 9). This peak does not correspond to warfarin sodium which has a $T_{max\ wt\ loss}$ of 313 ± 5 °C (Figure 10). This indicates that the majority of the residue (if not all) represents other chemical compounds that are likely used as a capping layer to encapsulate the dose of active pharmaceutical compound within the tablet until the time of use. The overlay plot of all treatments is presented in Appendix B (Figure B-1).

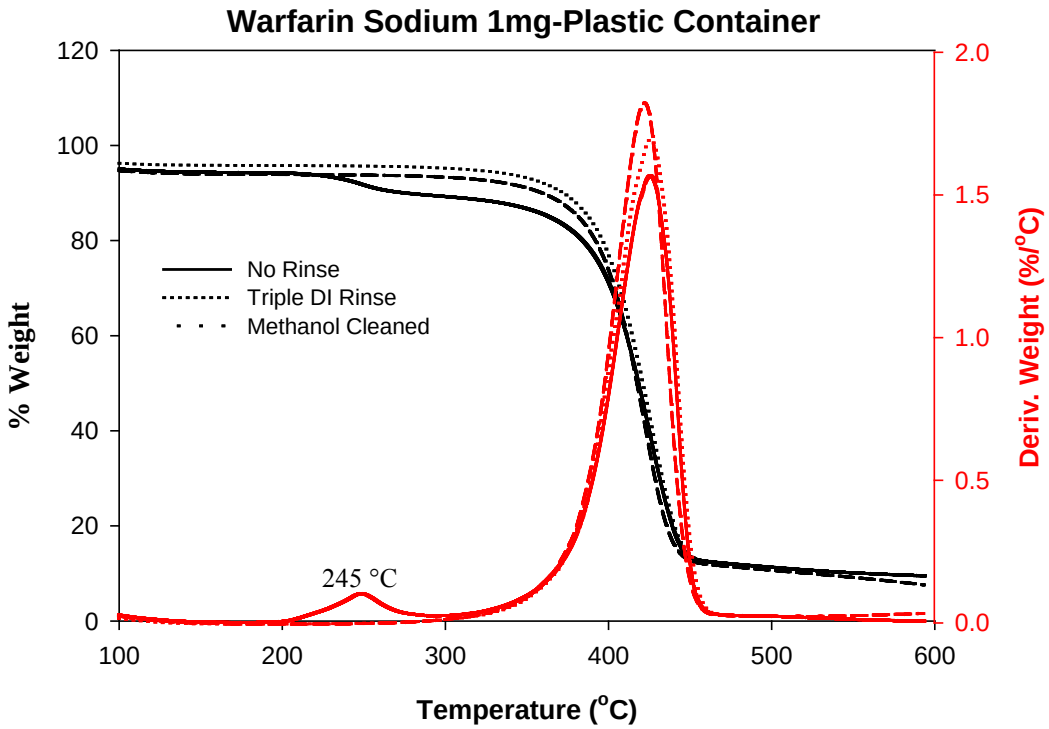


Figure 9. TGA results of Warfarin Sodium 1 mg, plastic containers

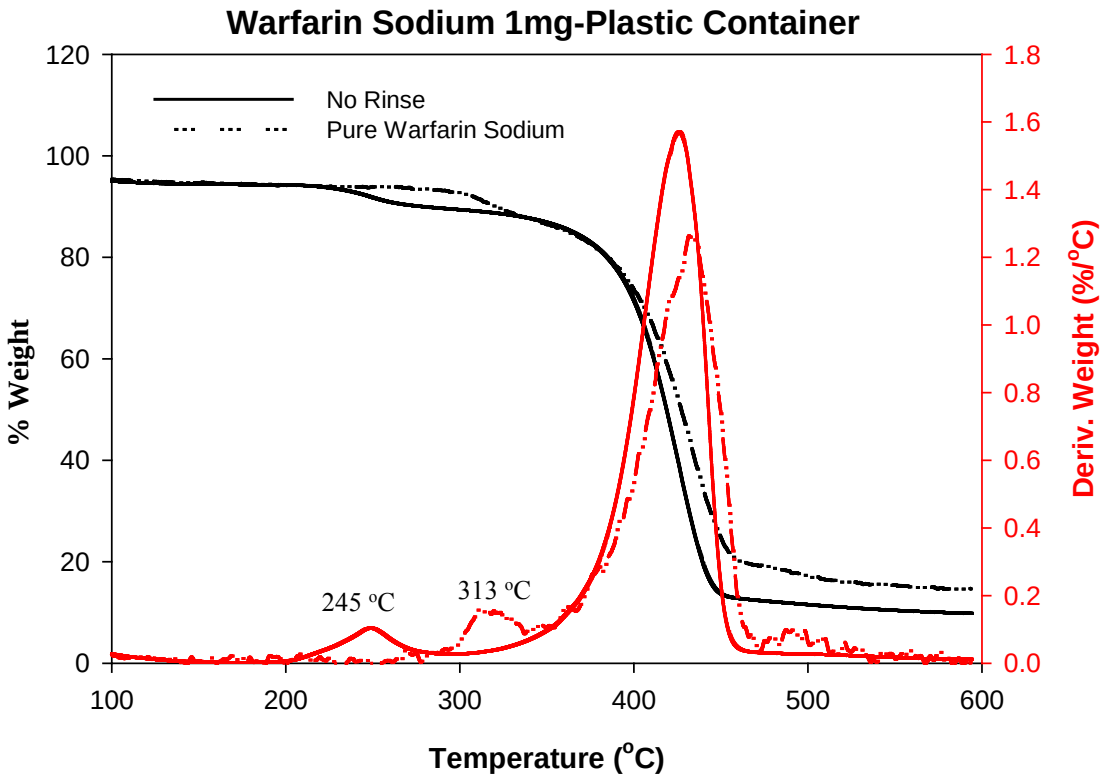
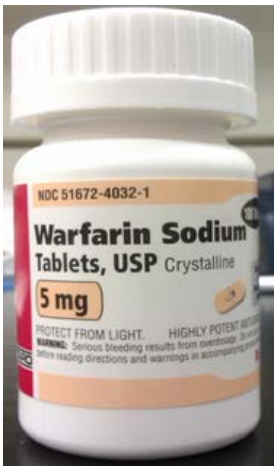


Figure 10. TGA results of non-rinsed containers of Warfarin Sodium 1 mg versus Warfarin Sodium

5.2.1.2 Mass Results

The amount of residuals/container =19.8 ± 0.9 mg (detailed calculations are presented in Appendix A, Table A-1). The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.0900 ± 0.0039 mg (Table A-2, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.2.2 Warfarin Sodium Tablets, 5mg



Medication: Warfarin Sodium Tablets, 5 mg

Active compound: Warfarin Sodium

Manufacturer: Taro Pharmaceutical Industries Ltd

Form: Tablets

Package: Plastic Container

Lot#:124320

Expiration Date: 08/2015; Date Received: 03/25/2013

5.2.2.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 239 °C for the non-rinsed containers (Figure 11). This peak does not correspond to warfarin sodium, which has a $T_{max\ wt\ loss}$ of 313 ± 5 °C (Figure 12). This indicates that the majority of the residues (if not all) represents other chemical compounds that are probably used as a capping layer to encapsulate the dose of active pharmaceutical compound within the tablet until the time of use. The overlay plot of all treatments is presented in Appendix B, Figure B-2.

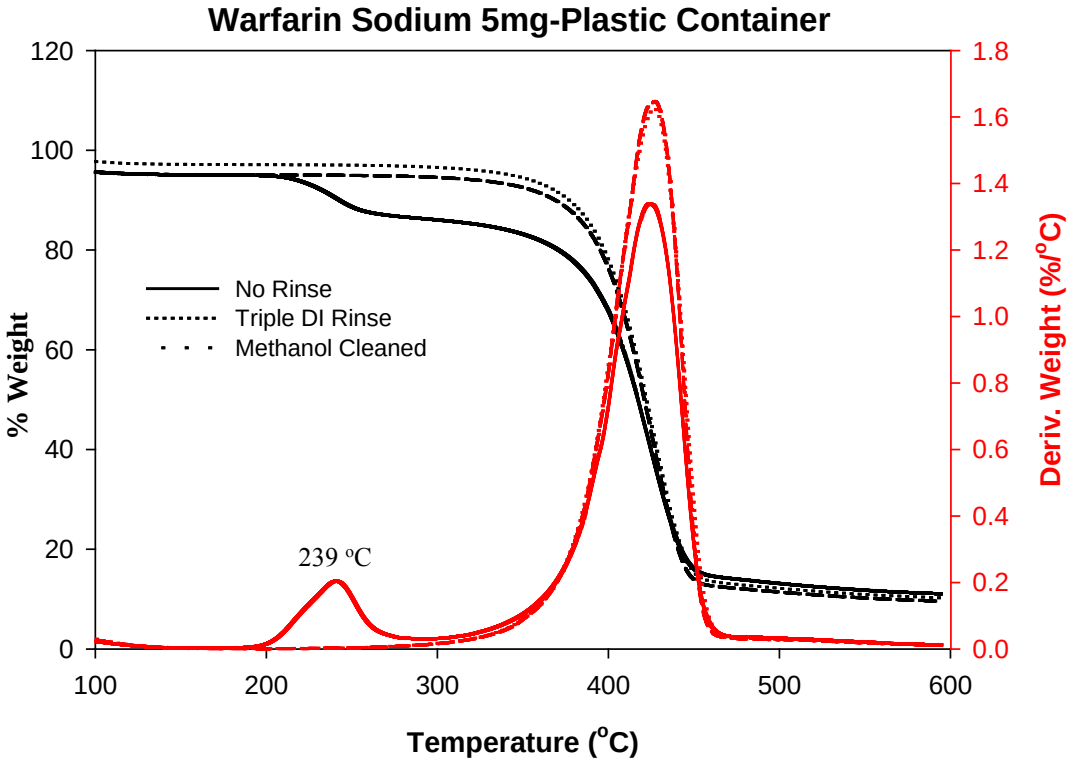


Figure 11. TGA results of Warfarin Sodium 5 mg, plastic containers

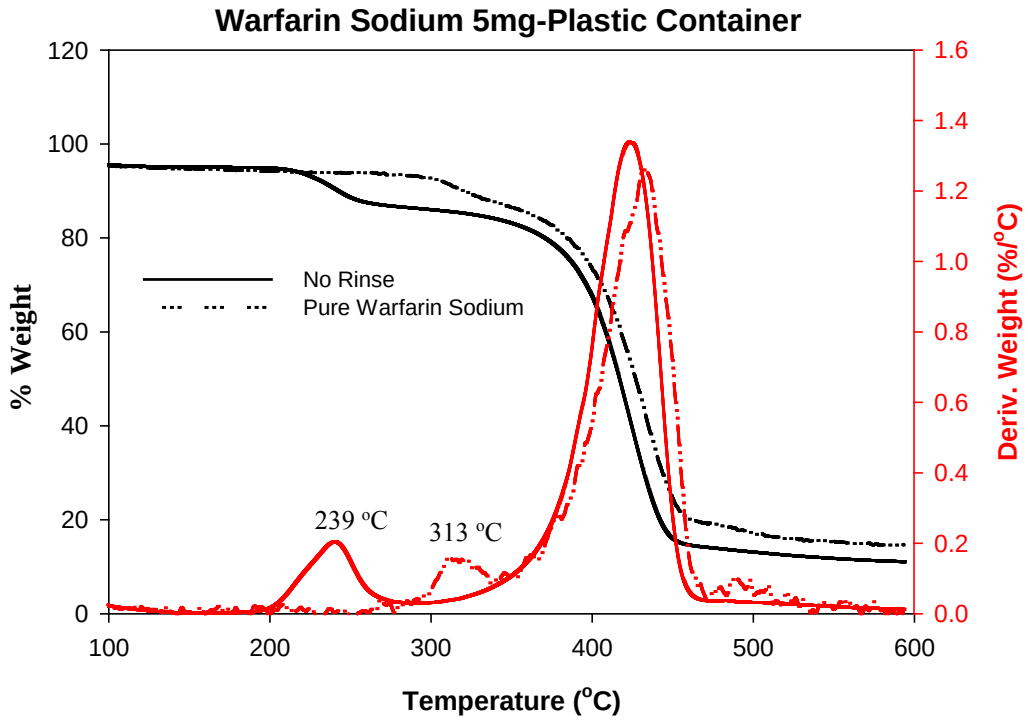


Figure 12. TGA results of non-rinsed containers of Warfarin Sodium 5 mg versus Warfarin Sodium

5.2.2.2 Mass Results

The amount of residuals/container =17.5 ± 1.1 mg (detailed calculations are presented in Appendix A, Table A-3). The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.3887 ± 0.0246 mg (Table A-4, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.2.3 Warfarin Sodium Tablets, 10mg

Medication: Warfarin Sodium Tablets, 10 mg

Active compound: Warfarin Sodium

Manufacturer: Taro Pharmaceutical Industries Ltd

Form: Tablets

Package: Plastic Container

Lot#:123976

Expiration Date: 08/2015

Date Received: 03/25/2013

5.2.3.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 231 °C for the non-rinsed containers (Figure 13). This peak does not correspond to warfarin sodium, which has a $T_{max\ wt\ loss}$ of 313 ± 5 °C (Figure 14). This indicates that the majority of the residues (if not all) represents other chemical compounds that are likely used as a capping layer to encapsulate the dose of active pharmaceutical compound within the tablet until the time of use. The overlay plot of all treatments is presented in Appendix B, Figure B-3.

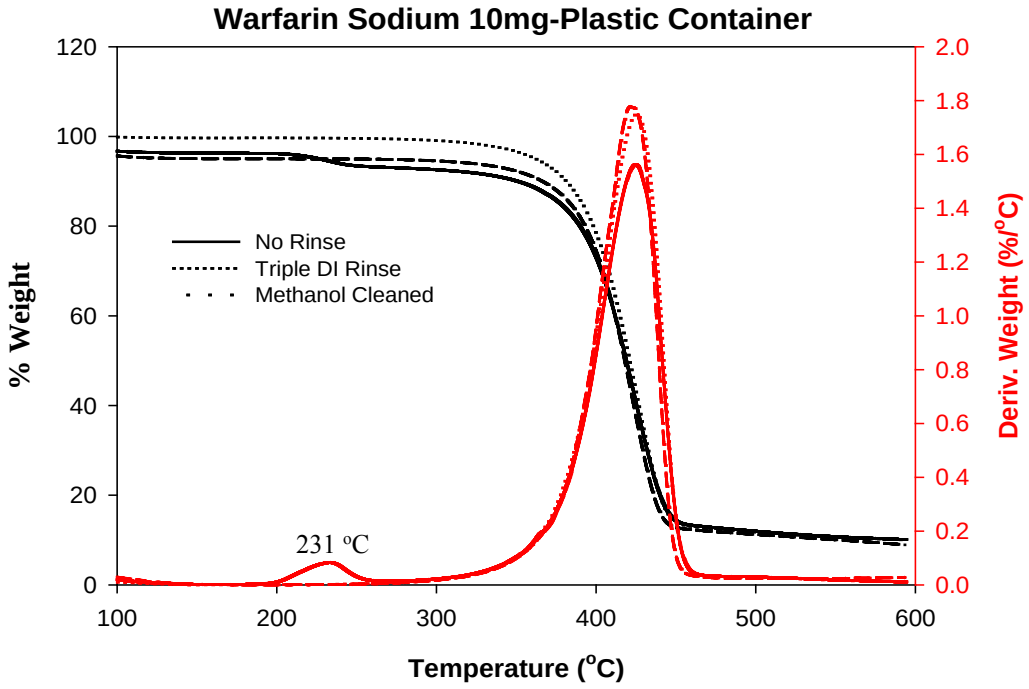


Figure 13. TGA results of Warfarin Sodium 10 mg, plastic containers

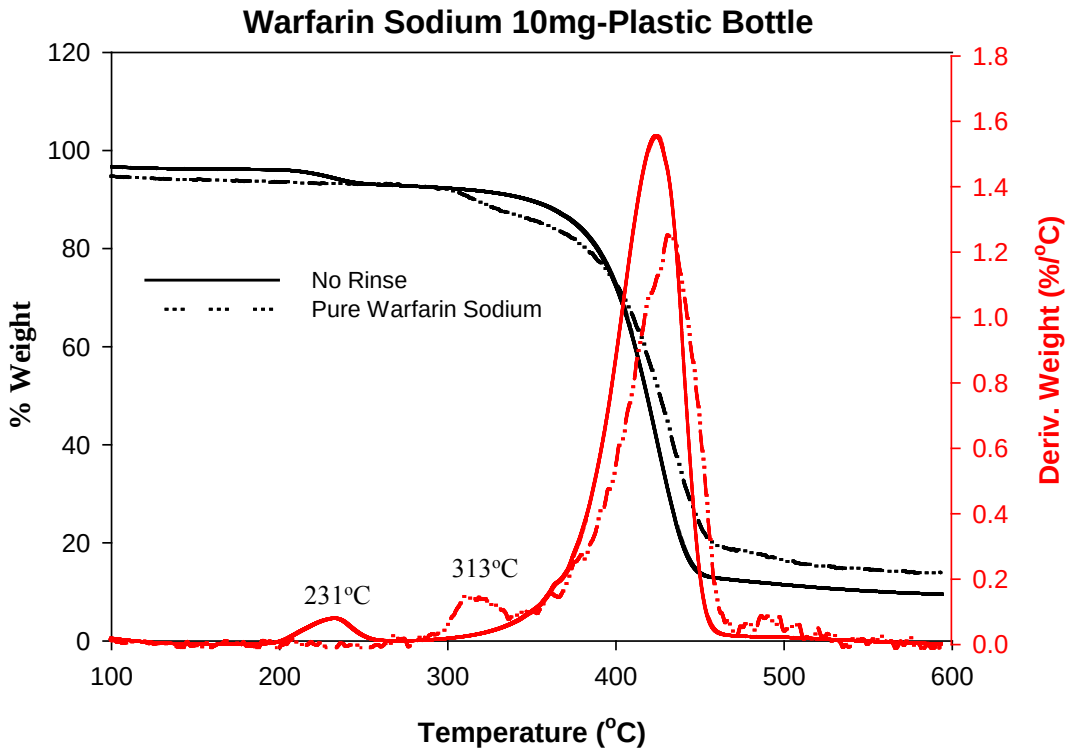
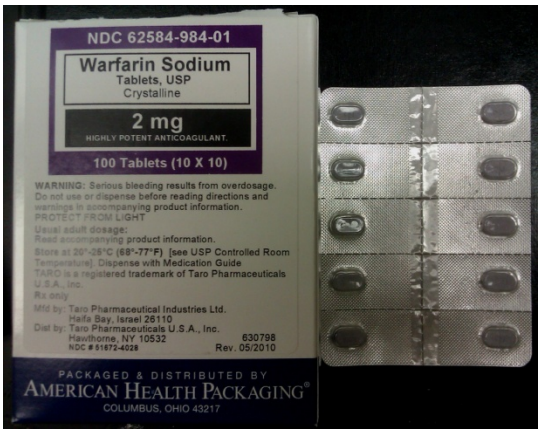


Figure 14. TGA results of non-rinsed containers of Warfarin Sodium 10 mg versus Warfarin Sodium

5.2.3.2 Mass Results

The amount of residuals/container =19.8 ± 1.2 mg (detailed calculations are presented in Appendix A, Table A-5). The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.8895 ± 0.0543 mg (Table A-6, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.2.4 Warfarin Sodium Tablets, 2mg



Active compound: Warfarin Sodium

Manufacturer: Taro Pharmaceutical Industries Ltd

Form: Tablets

Package: Blister Pack

Lot#:123247

Expiration Date: 09/2014

Date Received: 03/25/2013

5.2.4.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 15). The overlay plot of all treatments is presented in Appendix B, Figure B-4.

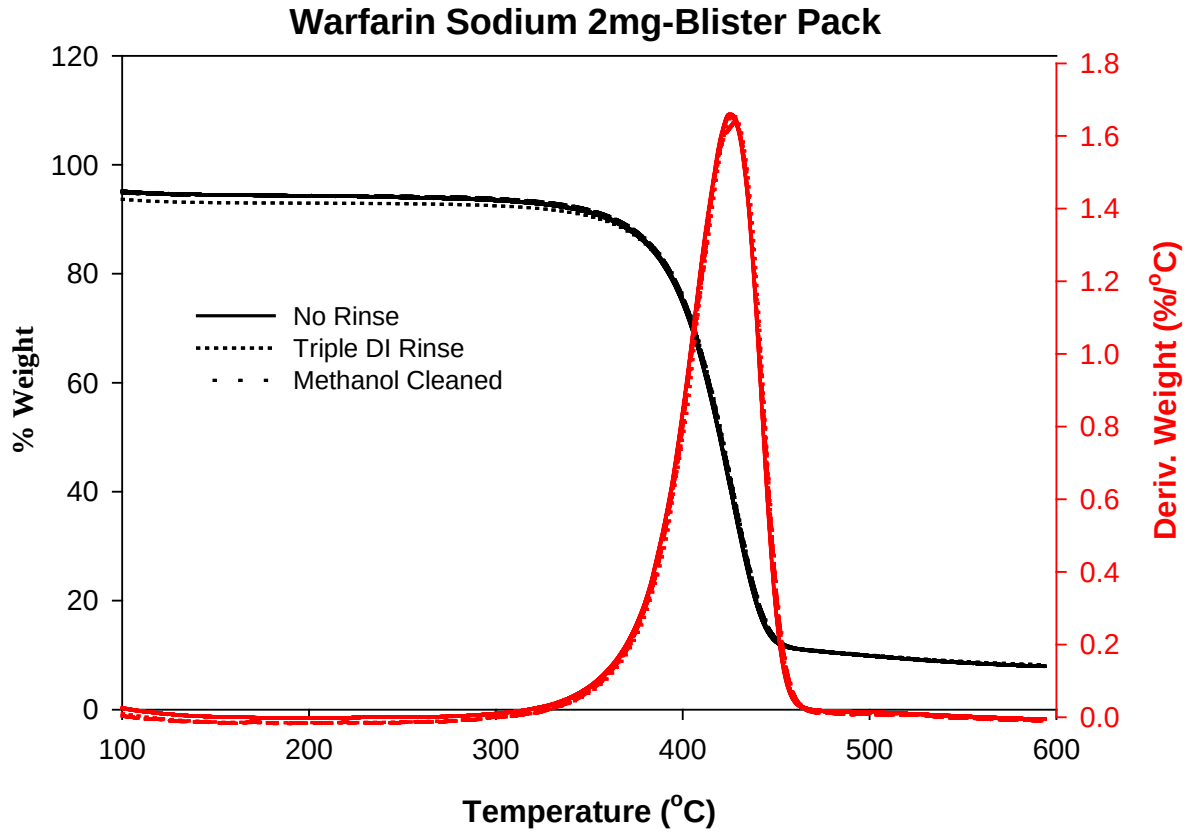


Figure 15. TGA results of Warfarin Sodium 2 mg, blister packs

5.2.4.2 Mass Results

The amount of residuals per one individual blister pack =0.3 ± 0.0 mg (detailed calculations are presented in Appendix A, Table A-7). This amount of residuals is within the range of the error of the balance.

The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.0026 ± 0.0002 mg (Table A-8, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.3 Jantoven

5.3.1 Jantoven Tablets, 1mg

Medication: Jantoven, 1mg

Active compound: Warfarin Sodium

Manufacturer: UPSHER-SMITH

Form: Tablets

Package: Blister Pack

Lot#: 307762

Expiration Date: 04/2014

Date Received: 03/25/2013

5.3.1.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 16). The overlay plot of all treatments is presented in Appendix B, Figure B-5.

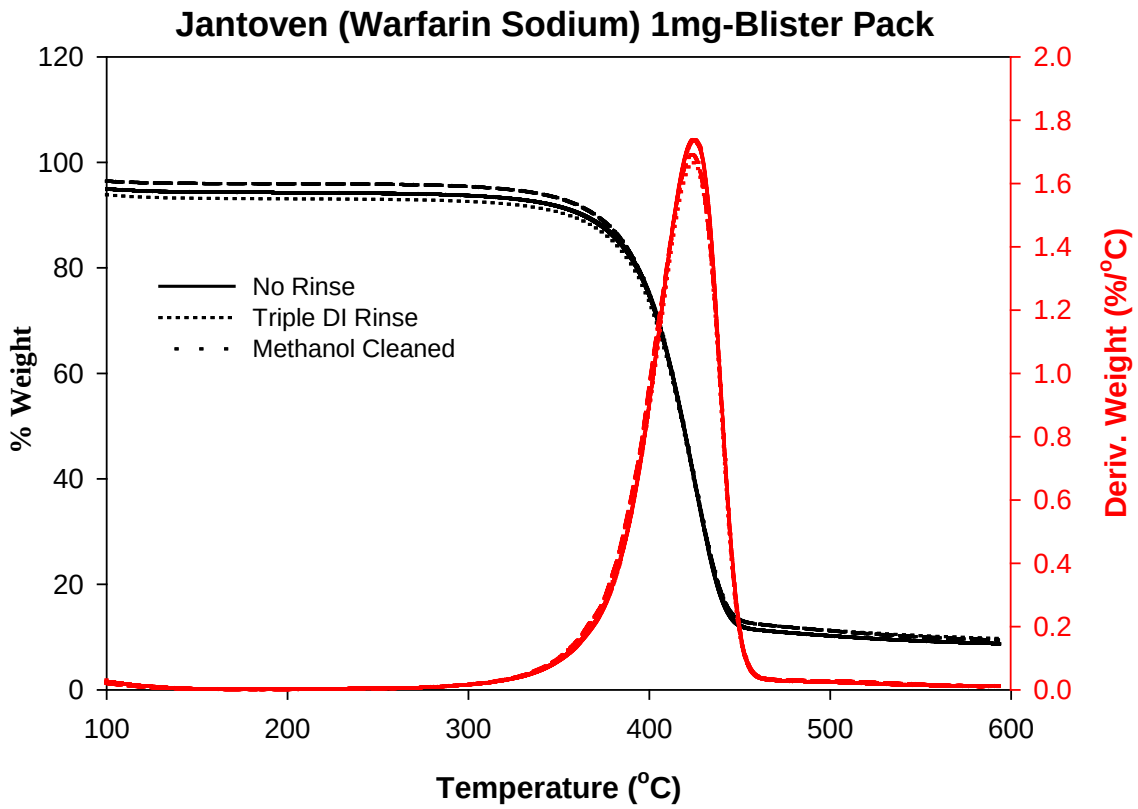


Figure 16. TGA results of Jantoven (Warfarin Sodium) 1 mg, blister packs

5.3.1.2 Mass Results

The amount of residuals per one individual blister pack =0.3 ± 0.0 mg (detailed calculations are presented in Appendix A, Table A-9). This amount of residuals is within the range of the error of the balance. The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.0012 ± 0.0001 mg (Table A-10, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.3.2 Jantoven Tablets, 10mg

Medication: Jantoven, 10mg

Active compound: Warfarin Sodium

Manufacturer: UPSHER-SMITH

Form: Tablets

Package: Blister Pack

Lot#: 308312

Expiration Date: 06/2014

Date Received: 03/25/2013

5.3.2.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 17). The overlay plot of all treatments is presented in Appendix B, Figure B-6.

5.3.2.2 Mass Results

The amount of residuals per one individual blister pack =0.2 ± 0.0 mg (detailed calculations are presented in Appendix A, Table A-11). This amount of residuals is within the range of the error of the balance.

The calculated upper limit for the amount of warfarin sodium in empty container residue is 0.0084 ± 0.0008 mg (Table A-12, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the tablets. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

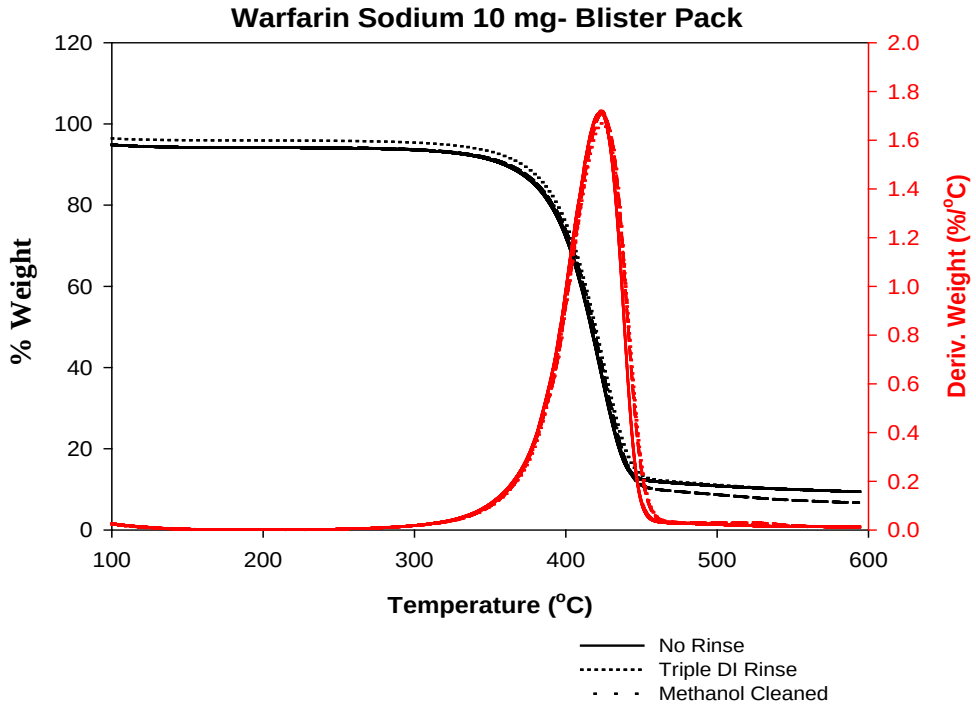


Figure 17. TGA results of Jantoven (Warfarin Sodium) 10 mg, blister packs

5.4 Nicotine

5.4.1 Nicorette Gum (Fruit Chill), 2mg

Medication: Nicorette Gum, 2mg

Active compound: Nicotine

Manufacturer: GlaxoSmithKline (GSK)

Form: Gums

Package: Blister Pack

Lot#: 12C28N

Expiration Date: 02/2015

Date Received: 03/25/2013

5.4.1.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 18). The overlay plot of all treatments is presented in Appendix B, Figure B-7.

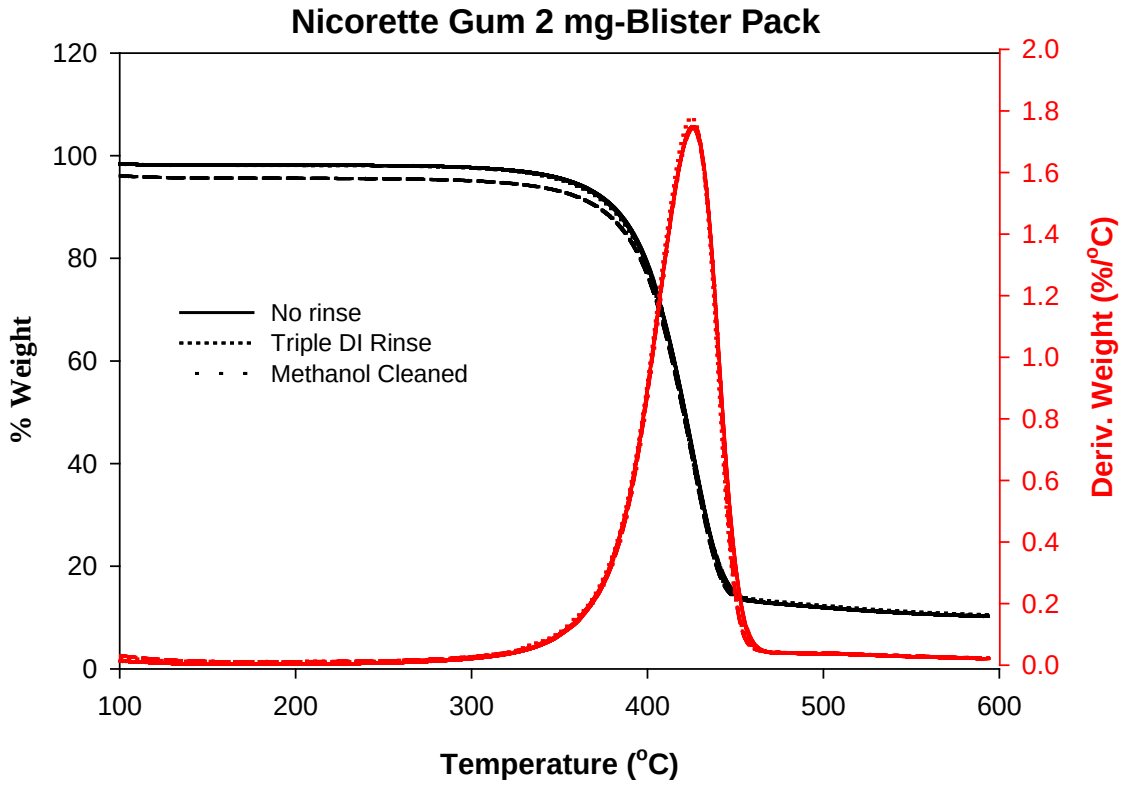


Figure 18. TGA results of Nicorette gum 2 mg, blister packs

5.4.1.2 Mass Results

The amount of residuals per one individual blister pack =0.3 ± 0.2 mg (detailed calculations are presented in Appendix A, Table A-13). This amount of residuals is within the range of the error of the balance.

The calculated upper limit for the amount of nicotine in empty container residue is 0.0005 ± 0.0002 mg (Table A-14, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the gums. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.4.2 Nicorette Gum (Fruit Chill), 4mg

Medication: Nicorette Gum, 4mg

Active compound: Nicotine

Manufacturer: GlaxoSmithKline (GSK)

Form: Gums

Package: Blister Pack

Lot#: 12L14N

Expiration Date: 10/2015

Date Received: 03/25/2013

5.4.2.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 19). The overlay plot of all treatments is presented in Appendix B, Figure B-8.

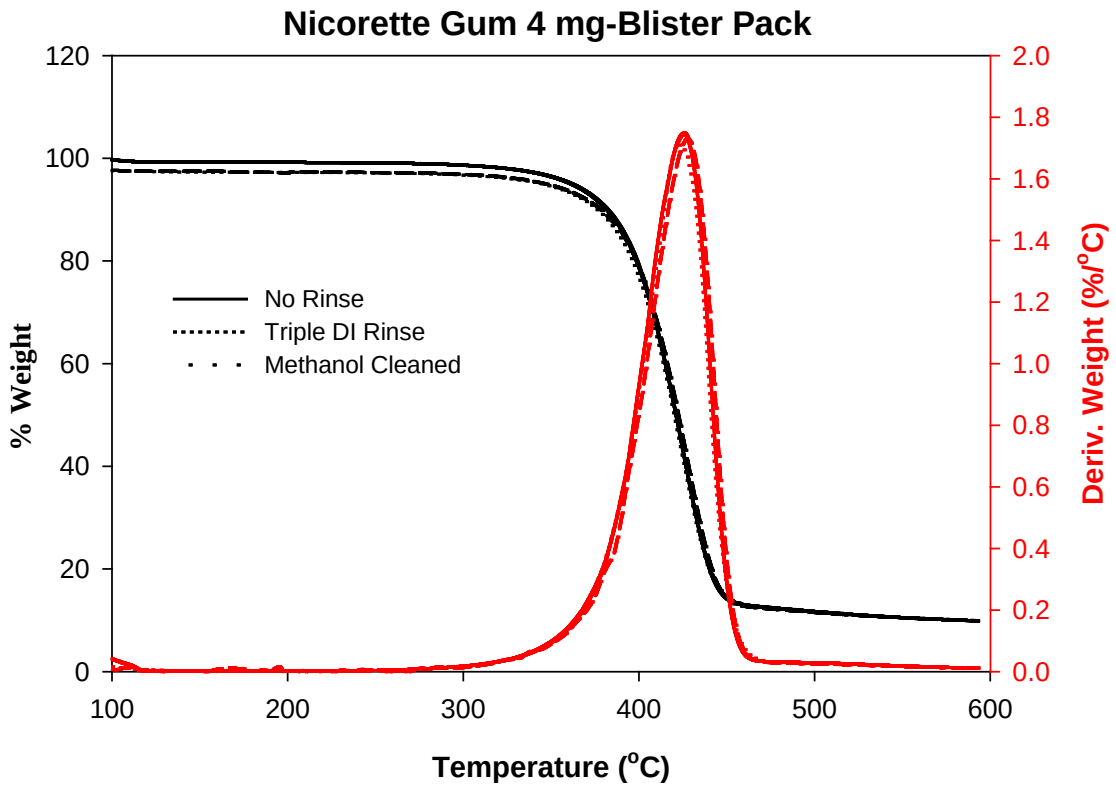


Figure 19. TGA results of Nicorette gum 4 mg, blister packs

5.4.2.2 Mass Results

The amount of residuals per one individual blister pack =0.3 ± 0.1 mg (detailed calculations are presented in Appendix A, Table A-15). This amount of residuals is within the range of the error of the balance.

The calculated upper limit for the amount of nicotine in empty container residue is 0.0008 ± 0.0002 mg (Table A-16, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the gums. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.4.3 Nicotine Polacrilex Gum, 2mg

Medication: Nicotine Polacrilex Gum, 2mg
Active compound: Nicotine

Manufacturer: Rugby Laboratories

Form: Gums

Package: Blister Pack

Lot#: 571893

Expiration Date: 08/2014

Date Received: 03/25/201

5.4.3.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 20). The overlay plot of all treatments is presented in Appendix B, Figure B-9.

5.4.3.2 Mass Results

The amount of residuals per one individual blister pack =0.1 ± 0.1 mg (detailed calculations are presented in Appendix A, Table A-17). This amount of residuals is within the range of the error of the balance.

The calculated upper limit for the amount of nicotine in empty container residue is 0.0002 ± 0.0002 mg (Table A-18, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the gums. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

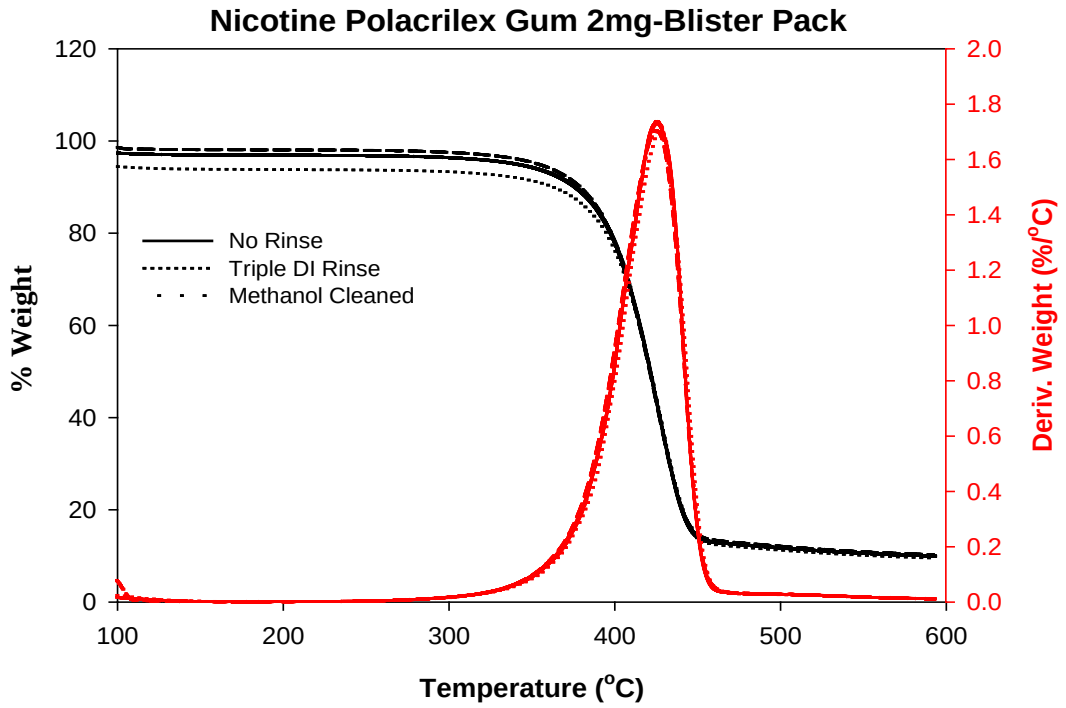
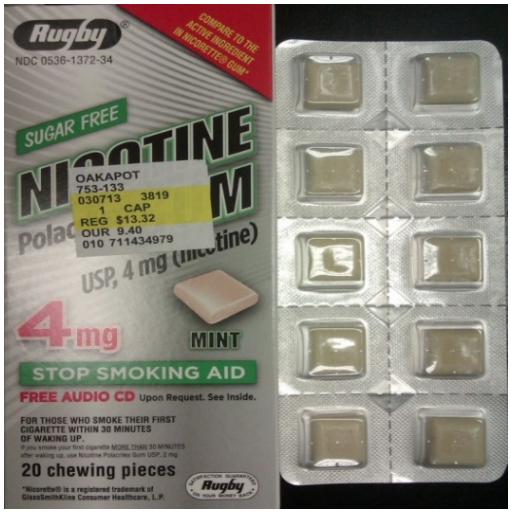


Figure 20. TGA results of Nicotine Polacrilex gum 2 mg, blister packs

5.4.4 Nicotine Polacrilex Gum, 4mg



Medication: Nicotine Polacrilex Gum, 4mg

Active compound: Nicotine

Manufacturer: Rugby Laboratories

Form: Gums

Package: Blister Pack

Lot#: 508965

Expiration Date: 04/2014

Date Received: 03/25/2013

5.4.4.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 21). The overlay plot of all treatments is presented in Appendix B, Figure B-10.

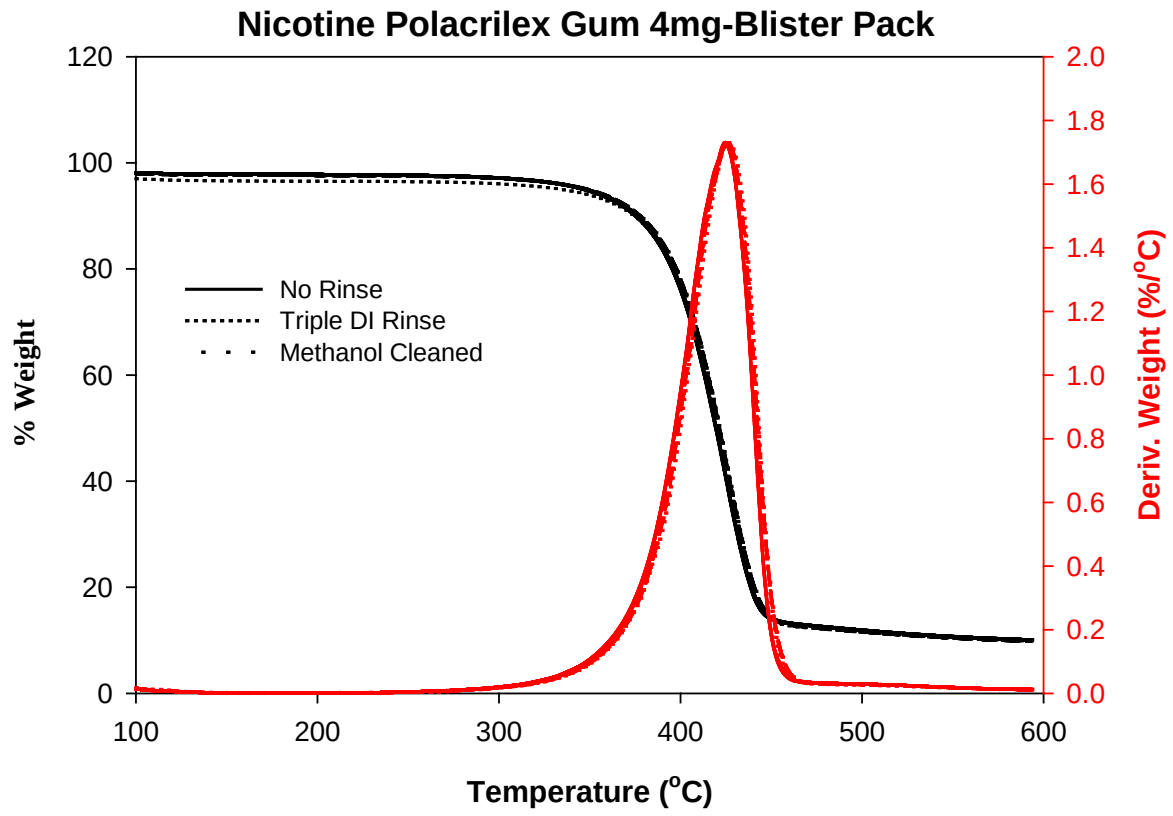


Figure 21. TGA results of Nicotine Polacrilex gum 4 mg, blister packs

5.4.4.2 Mass Results

The amount of residuals per one individual blister pack =0.1 ± 0.1 mg (detailed calculations are presented in Appendix A, Table A-19). This amount of residuals is in the range of the error of the balance.

The calculated upper limit for the amount of nicotine in empty container residue is 0.0003 ± 0.0002 mg (Table A-20, Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the gums. This assumption represents the worst case scenario. In reality, the outer layer of the medication probably does not contain the drug; rather, it may be a coating that is needed to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

5.4.5 Nicorette Mini Lozenge, 2mg

Medication: Nicorette Mini Lozenge, 2mg

Active compound: Nicotine

Manufacturer: GlaxoSmithKline (GSK)

Form: Lozenge

Package: Plastic Container

Lot#: 14149

Expiration Date: 04/2015

Date Received: 08/13/2013

5.4.5.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 306 ºC for the non-rinsed containers (Figure 22). This peak does not correspond to nicotine, which has a $T_{max\ wt\ loss}$ of 217 ± 5 ºC (Figure 23). This indicates that the majority of the residues (if not all) represents other chemical compounds that are likely used as a capping layer to encapsulate the dose of active pharmaceutical compound within the lozenge until the time of use. The overlay plot of all treatments is presented in Appendix B, Figure B-11.

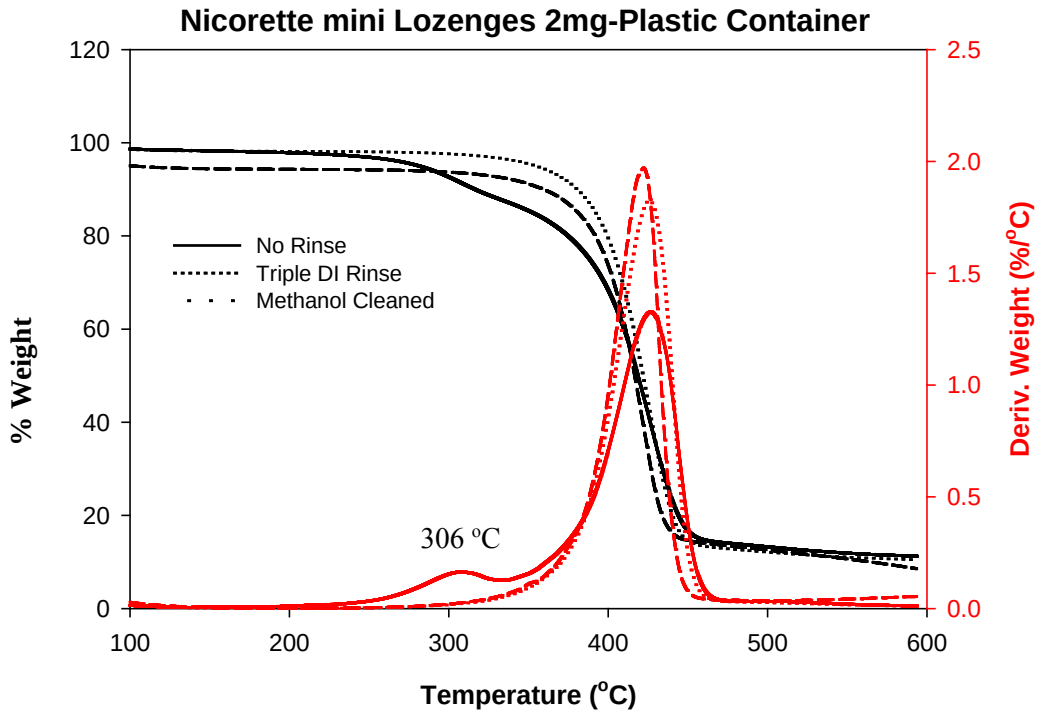


Figure 22. TGA results of Nicorette mini lozenges 2 mg, plastic containers

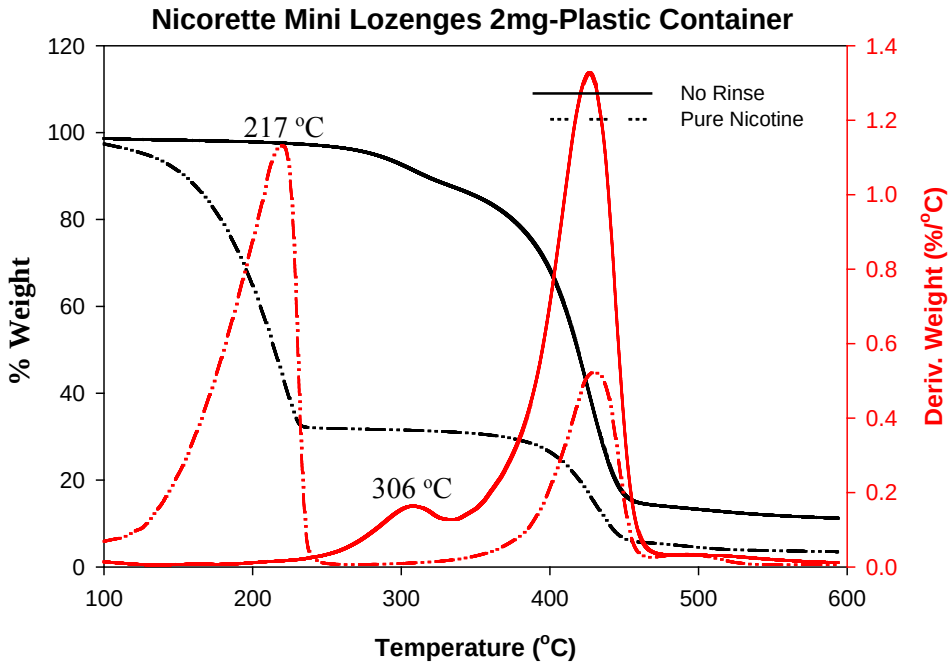


Figure 23. TGA results of Nicorette mini lozenges 2 mg plastic containers versus pure nicotine

5.4.5.2 Mass Results

The amount of residuals/container =0.2 mg (detailed calculations are presented in Appendix A, Table A-21). This amount of residuals is within the range of the error of the balance. It is noted that residuals could be visually seen in the empty containers after the disposal of the lozenges. But the weight of the residual was negligible as compared to the relatively large container weight, and thus, the residuals were not detectable by the balance. The density of the residuals could also be very low which may be also part of the problem. The presence of peaks for the residuals from the TGA analysis supports the presence of a significantly larger quantity of residuals as compared to the weight obtained by the balance.

Therefore, the balance results for this medication are misleading and should not be used. Only duplicate samples were tested from this medication for each treatment. This was a result of the limited quantity of medication from the vendor.

5.4.6 Nicorette Lozenge, 4mg

Medication: Nicorette Lozenge, 4mg

Active compound: Nicotine

Manufacturer: GlaxoSmithKline (GSK)

Form: Lozenge

Package: Plastic Container

Lot#:13674

Expiration Date: 05/2014

Date Received: 03/25/2013

5.4.6.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 324 °C for the non-rinsed containers (Figure 24). This peak does not correspond to nicotine, which has a $T_{max\ wt\ loss}$ of 217 ± 5 °C (Figure 25). This indicates that the majority of the residues (if not all) represents other chemical compounds that are likely used as a capping layer to encapsulate the dose of active pharmaceutical compound within the lozenge until the time of use. The overlay plot of all treatments is presented in Appendix B, Figure B-12.

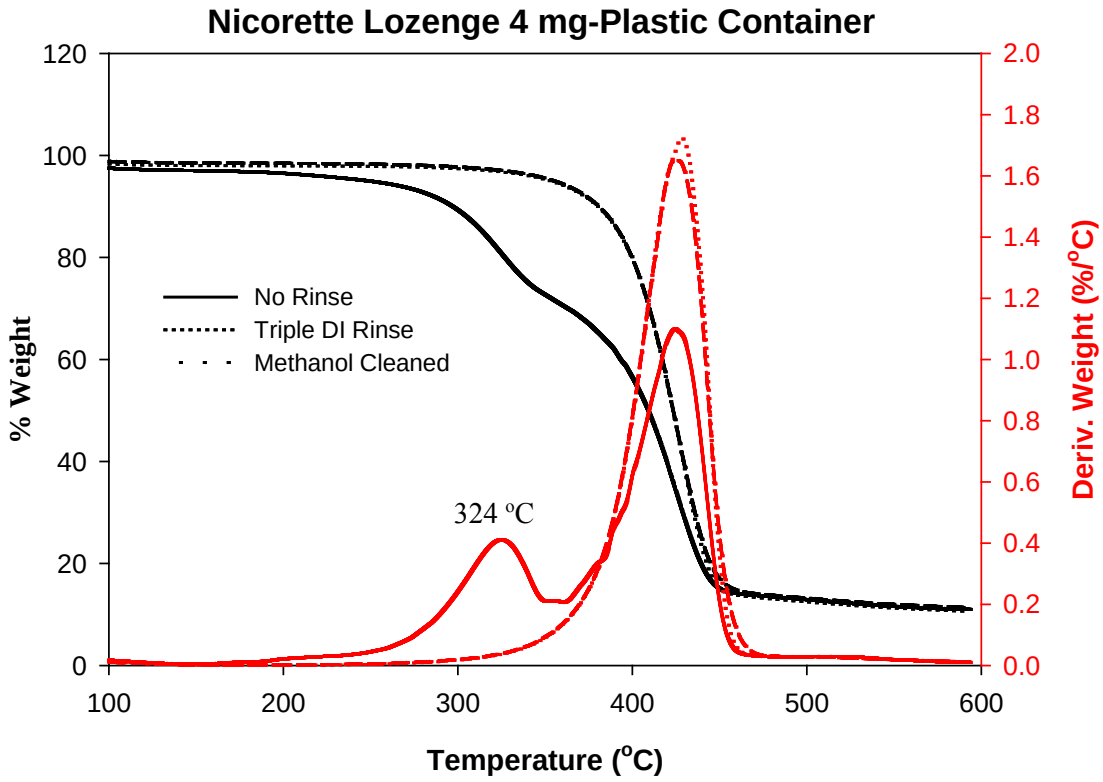


Figure 24. TGA results of Nicorette lozenges 4 mg, plastic containers

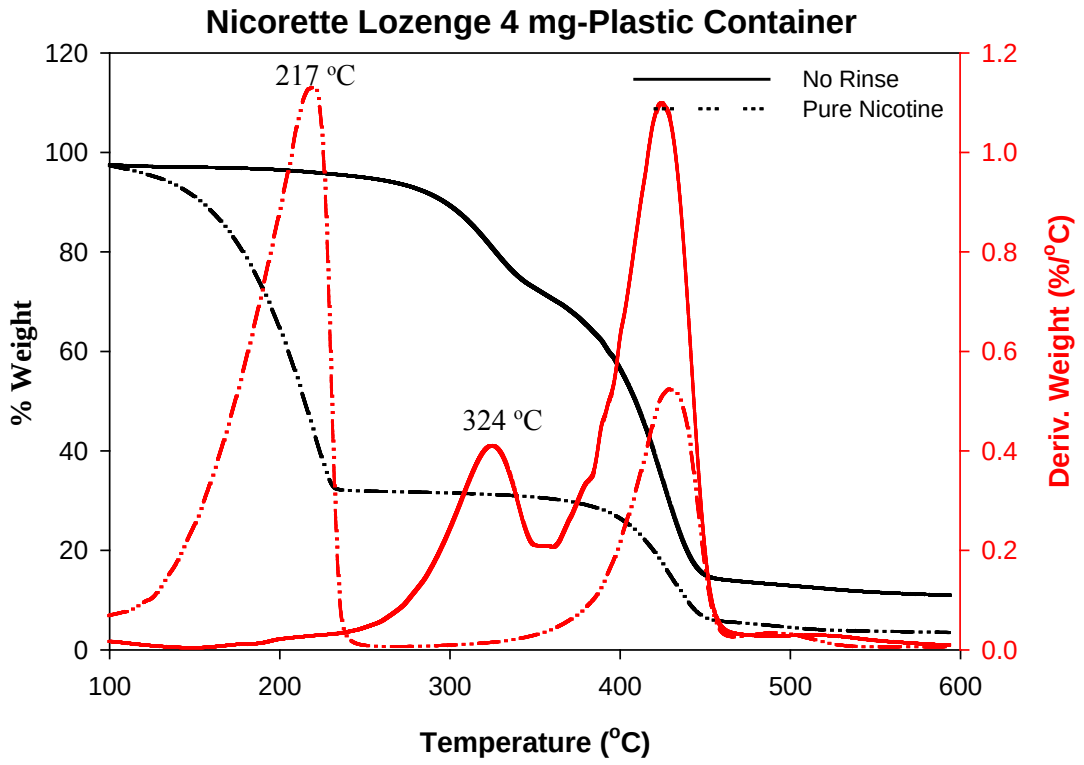
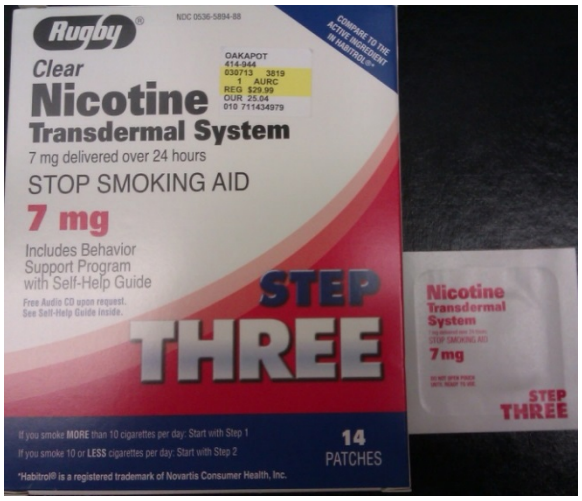


Figure 25. TGA results of Nicorette lozenges 4 mg, plastic containers versus pure nicotine

5.4.6.2 Mass Results

The amount of residuals/container =0.0 ± 0.0 mg (detailed calculations are presented in Appendix A, Table A-22). This amount of residuals is within the range of the error of the balance. It is noted that residuals could be visually seen in the empty containers after the disposal of the lozenges. But the weight of the residual was negligible when compared to the relatively large container weight, and thus, the residuals were not detectable by the balance. The density of the residuals could also be very low, which may be also part of the problem. The presence of peaks for the residuals from the TGA analysis supports the presence of a significantly larger quantity of residuals as compared to the weight obtained by the balance. Therefore, the balance results for this medication are misleading, and should not be used.

5.4.7 Nicotine Transdermal System (Patch), 7mg



Medication: Nicotine Transdermal System, 7mg

Active compound: Nicotine

Manufacturer: Rugby Laboratories

Form: Patch

Package: Plastic Wrap (peel off)

Lot#: 40660

Expiration Date: 05/2014

Date Received: 03/25/2013

Figure 26. Picture of the Nicotine patches

5.4.7.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 27). The overlay plot of all treatments is presented in Appendix B, Figure B-13.

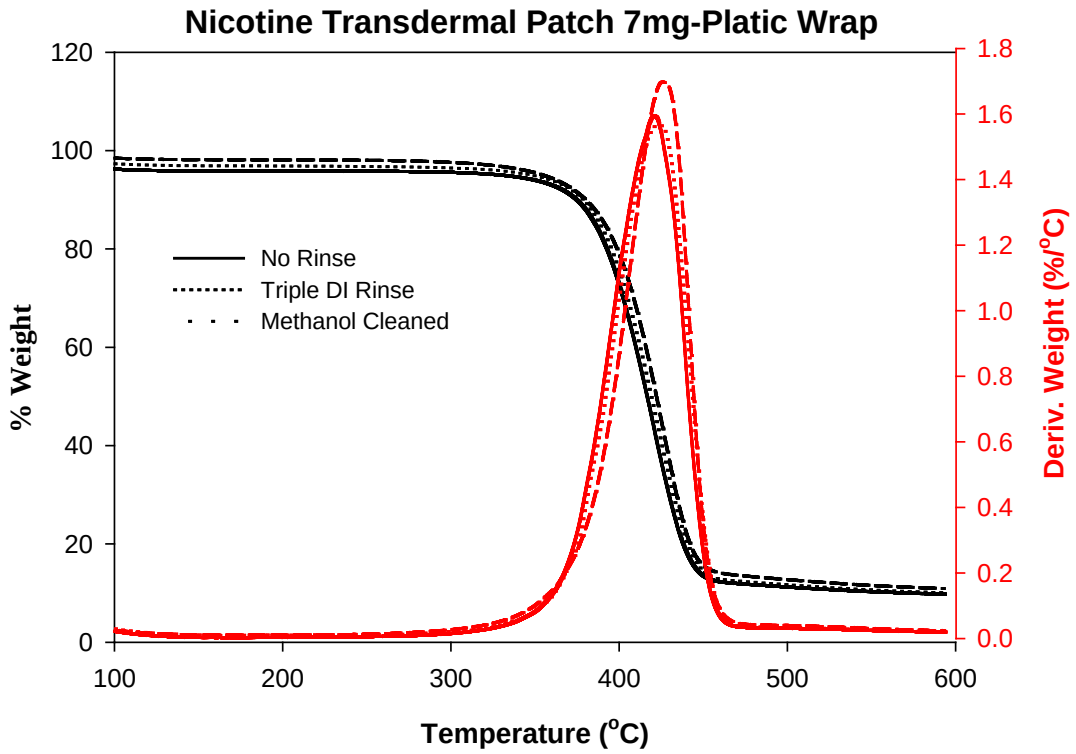
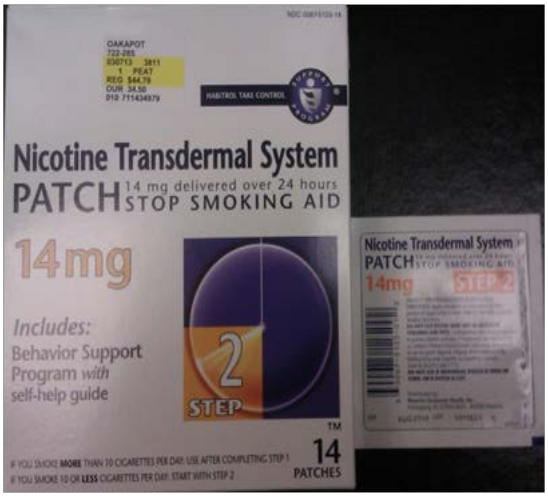


Figure 27. TGA results of Nicotine Transdermal Patches 7 mg, plastic wrap

5.4.7.2 Mass Results

The amount of residuals/container =0.1 ± 0.2 mg (detailed calculations are presented in Appendix A, Table A-23). This amount of residuals is within the range of the error of the balance. The calculated upper limit for the amount of nicotine in empty container residue was 0.0011± 0.0026 mg (Table A-24, Appendix A). This amount was calculated assuming that the drug is distributed evenly across the surface of the patch along with other chemicals that ensure the active ingredient's slow release over a 24-hour time period.

5.4.8 Nicotine Transdermal System (Patch), 14mg



Medication: Nicotine Transdermal System, 14mg

Active compound: Nicotine

Manufacturer: Habitrol

Form: Patch

Package: Plastic Wrap (peel off)

Lot#:121356

Expiration Date: 08/2014; Date Received: 03/25/2013

5.4.8.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 28). The overlay plot of all treatments is presented in Appendix B, Figure B-14.

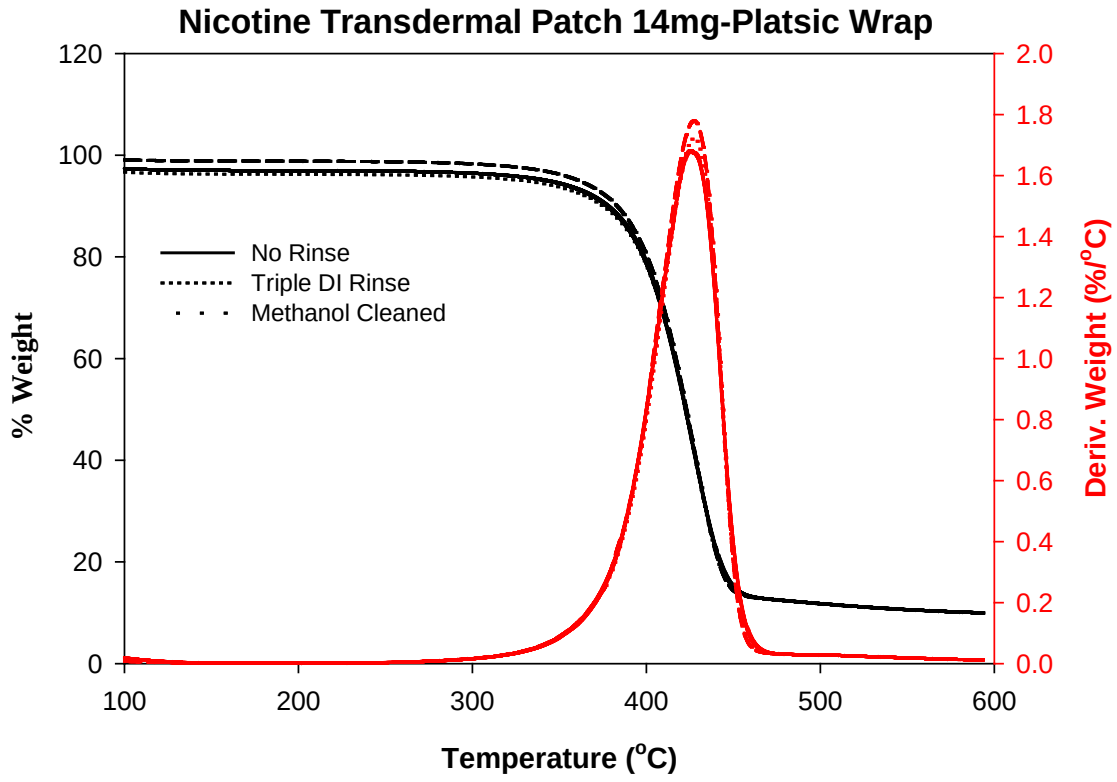
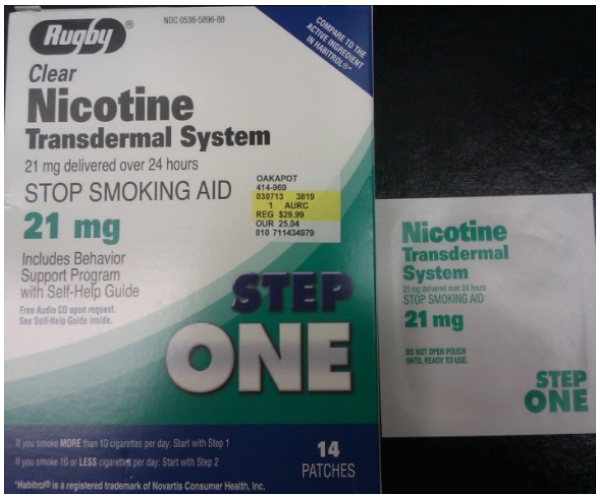


Figure 28. TGA results of Nicotine Transdermal Patches 14 mg, plastic wrap

5.4.8.2 Mass Results

The amount of residuals/container =0.0 ± 0.0 mg (detailed calculations are presented in Appendix A, Table A-25). This amount of residuals is within the range of the error of the balance. The calculated upper limit for the amount of nicotine in empty container residue is 0.0000 ± 0.0000 mg (Table A-26, Appendix A). This amount is calculated assuming that the drug is distributed evenly across the surface of the patch.

5.4.9 Nicotine Transdermal System (Patch), 21mg



Medication: Nicotine Transdermal System, 21mg

Active compound: Nicotine

Manufacturer: Rugby Laboratories

Form: Patch

Package: Plastic Wrap (peel off)

Lot#: 40703

Expiration Date: 05/2015

Date Received: 03/25/2013

5.4.9.1 Thermogravimetric Results

There was no $T_{max\ wt\ loss}$ peak for the residuals in the non-rinsed containers (Figure 29). The overlay plot of all treatments is presented in Appendix B, Figure B-15.

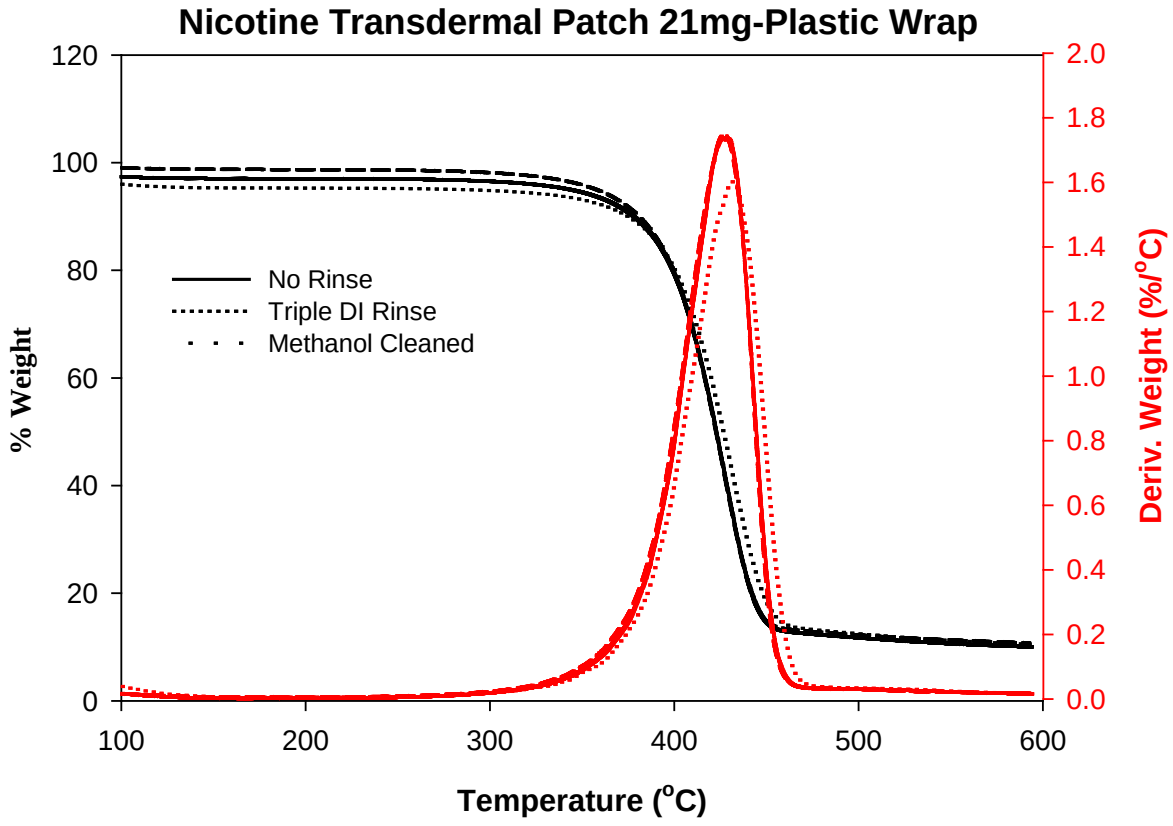


Figure 29. TGA results of Nicotine Transdermal Patches 21 mg, plastic wrap

5.4.9.2 Mass Results

The amount of residuals/container =0.0 ± 0.1 mg (detailed calculations are presented in Appendix A, Table A-27). This amount of residuals is within the range of the error of the balance. The calculated upper limit for the amount of nicotine in empty container residue is 0.0000 ± 0.0010 mg (Table A-28, Appendix A). This amount is calculated assuming that the drug is evenly distributed across the surface of the patch.

5.4.10 Nicotrol NS (nicotine nasal spray), 10mg/ml

Medication: Nicotrol NS, 10 mg/ml

Active compound: Nicotine

Manufacturer: Pfizer

Form: Liquid

Package: Glass Vial

Lot#: PH111G

Expiration Date: 08/2014

Date Received: 03/25/2013

5.4.10.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 217 ºC for the non-rinsed containers (Figure 30). This peak corresponds to pure nicotine, which has a $T_{max\ wt\ loss}$ of 217 ± 5 ºC (Figure 31). The overlay plot of all treatments is presented in Appendix B, Figure B-16.

It must be noted that in the case of the non-rinsed containers, the residuals of this medication were in liquid form. The $T_{max\ wt\ loss}$ for the cotton piece of the non-rinsed containers (used as a QA/QC) was 410 ºC, which is not within the acceptable range (427 ± 5 ºC). This deviation was not due to a calibration problem because the triple-rinsed and the clean containers were analyzed on the TGA right after the non-rinsed containers and the $T_{max\ wt\ loss}$ for the cotton piece were within the specified range. The deviation that occurred for these samples may be a result of a reaction between the residual liquid and the cotton piece, which may have resulted in changes in the properties of the cotton piece. Therefore, the TGA results of this medication are inconclusive. Nonetheless, the fact that this medication is in liquid from and contains

67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ºC represents nicotine.

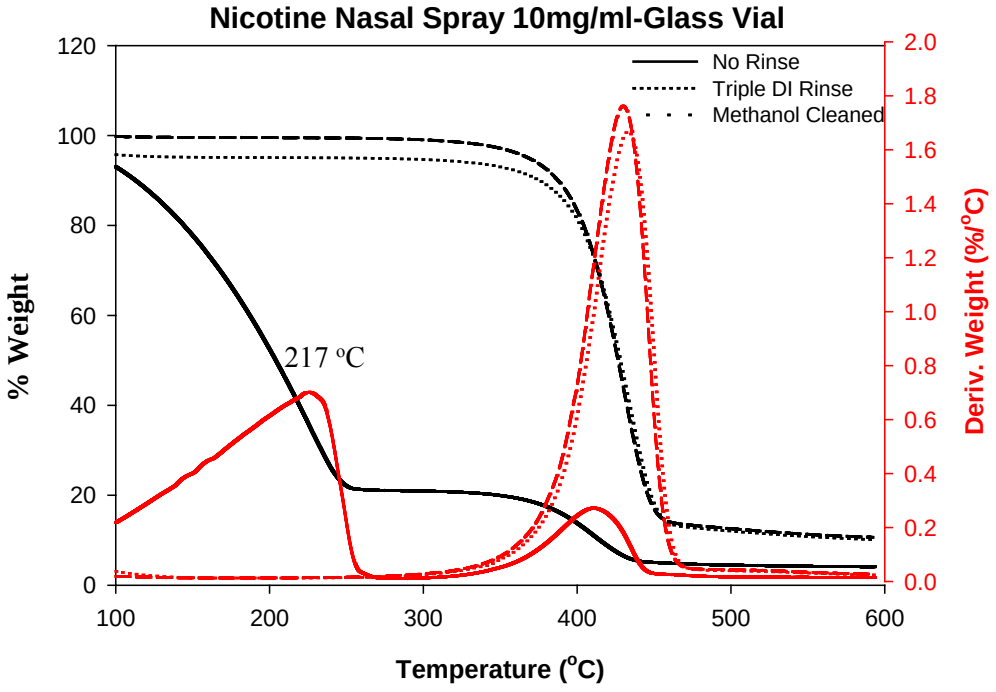


Figure 30. TGA results of Nicotine nasal spray 10 mg/ml, glass vial

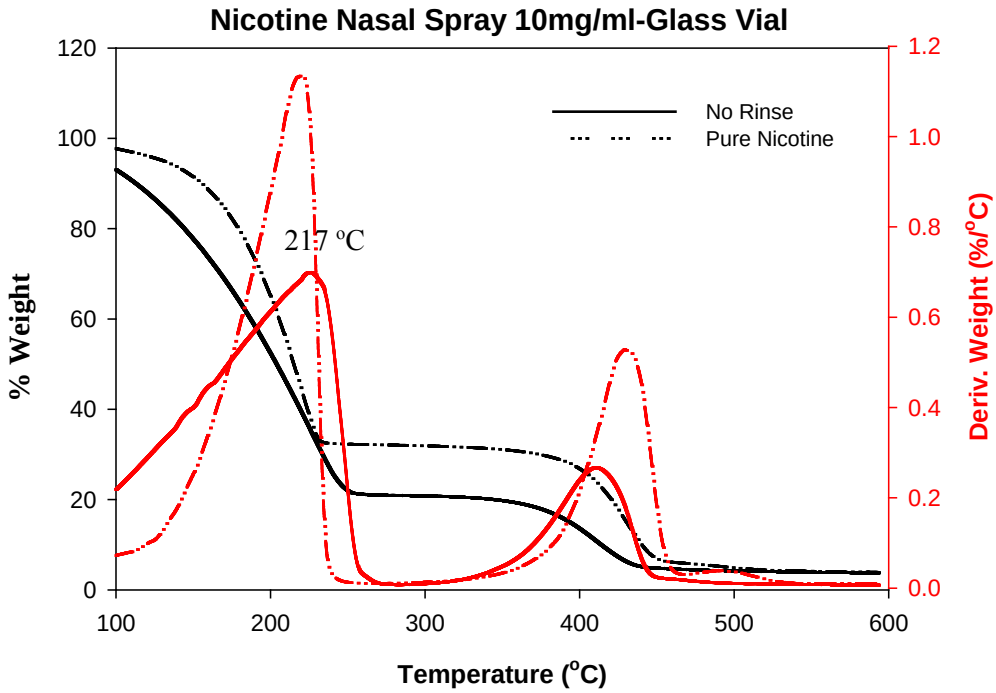


Figure 31. TGA results of Nicotine nasal spray 10 mg/ml, glass vial versus pure Nicotine

5.4.10.2 Mass Results

The amount of residuals/vial =67.8 ± 36.9 mg (detailed calculations are presented in Appendix A, Table A-29). The high standard deviation in this case is a result of the nature of the medication. The medication is in liquid form, and therefore, when removing the medication from the container, the remaining liquid is expected to have significant differences from one container to the other when emptying the container when trying to simulate the use. The calculated amount of nicotine in empty container residue is 0.6780 mg (Appendix A). This amount is calculated assuming that the drug is homogenously distributed in the glass vial, which is highly likely since the sample is in liquid form.

5.4.11 Nicotrol Inhaler (nicotine inhalation system), 10mg/cartridge

Medication: Nicotrol Inhaler, 10 mg/cartridge

Active compound: Nicotine

Manufacturer: Pfizer

Form: Cartridge

Package: Plastic Container

Lot#: PA068A

Expiration Date: 01/2015

Date Received: 03/25/2013

The amount of residuals/cartridge =6 mg. This value is not experimentally determined for two reasons:

1. The manufacturer already mentioned on the package that every cartridge contains 10 mg nicotine, with 4 mg of the drug delivered (please see the above picture).
2. Simulation of the use of this medication was not possible in the laboratory.

Therefore, no experiments (balance or TGA) were conducted on this medication because it is already known how much nicotine will be in the residuals. It should be noted that at temperatures higher than room temperatures, more nicotine can be released from the cartridge. Nonetheless, 6 mg is a conservative upper estimate for the level of nicotine residue in the cartridge.

5.5 Physostigmine Salicylate Medications

5.5.1 Physostigmine Salicylate, (1mg/ml)

Medication: Physostigmine Salicylate injection, 1mg/ml
Active compound: Physostigmine Salicylate

Manufacturer: Akron Inc.

Form: liquid for injection

Package: Glass Ampoule

Lot#:101402

Expiration Date: 10/2014

Date Received: 03/25/2013

5.5.1.1 Thermogravimetric Results

The average $T_{max\ wt\ loss}$ for the residuals was 103 ºC for the non-rinsed containers (Figure 32). This peak does not correspond to physostigmine salicylate, which has a $T_{max\ wt\ loss}$ of 236 ± 5 ºC (Figure 33). The overlay plot of all treatments is presented in Appendix B, Figure B-17.

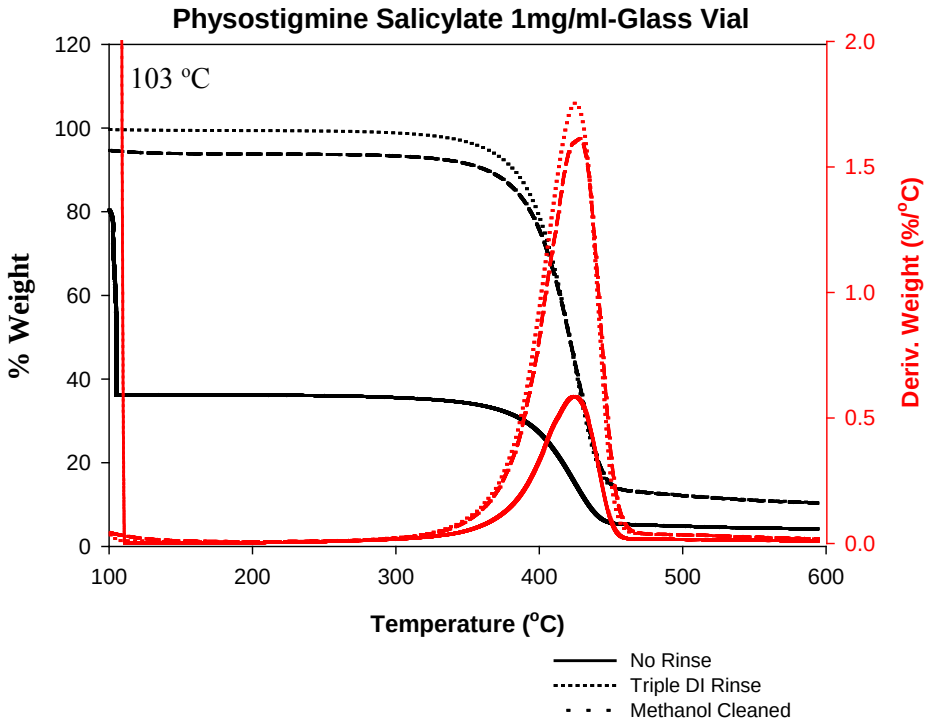


Figure 32. TGA results of Physostigmine Salicylate 1 mg/ml, glass vial

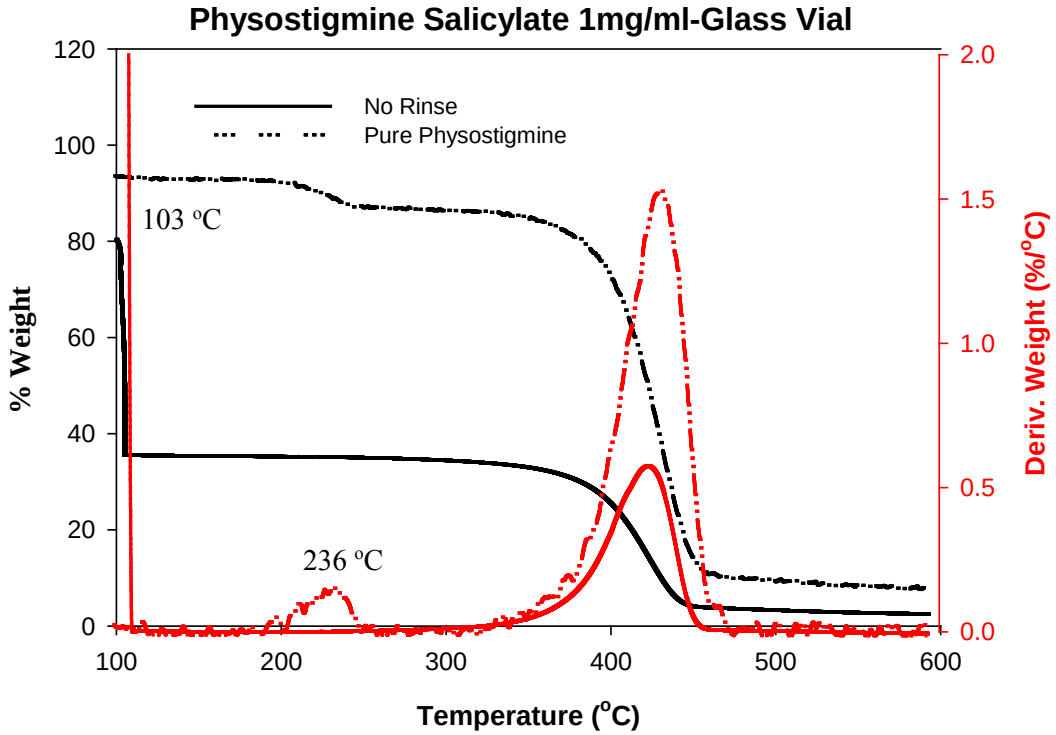


Figure 33. TGA results of Physostigmine Salicylate 1 mg/ml, glass vial versus pure Physostigmine Salicylate

5.5.1.2 Mass Results

The amount of residuals/vial =73.0 ± 2.2 mg (detailed calculations are presented in Appendix A, Table A-30). This means that the volume of residuals equals ~ 73 uL. Thus, if the concentration of the active drug is 1mg/ml, then the amount of physostigmine in the residual per vial is = 0.0730 ± 2.2000 mg.

6 Quality Control

6.1 Accuracy (bias)

The current study was conducted under a Quality Assurance Project Plan (QAPP) that was approved by the U.S. EPA with a QA ID # L18039-QP-1-5 (Appendix D). A summary of the required QA/QC checks for accuracy and whether or not the accuracy was met are presented in Table 2.

For the measurements of the weight of residuals, the accuracy checks for the balance AB104-S (Mettler Toledo) as well as the TGA balance were conducted as specified in Table 2 and were recorded in the project laboratory notebook CH 276.

The accuracy of the TGA (TA 2950) temperature measurements were verified for each of the analyzed samples by checking that the $T_{max\ wt\ loss}$ for the cotton piece for each sample was within the range specified in the QAPP (427 ± 5 °C). The $T_{max\ wt\ loss}$ values of the cotton piece of all the analyzed samples on the TGA are presented in Table C-1 (Appendix C). The $T_{max\ wt\ loss}$ of the cotton piece was in the acceptable range for all samples except the triplicate samples of the non-rinsed containers of nicotine nasal spray 10 mg/ml. This discrepancy was not a result of a calibration issue because cotton peaks of the triple rinsed samples of nicotine nasal spray were in agreement with the specified range though they were analyzed right after the analysis of the non-rinsed samples on the same day (August 20, 2013). The reason for this discrepancy may be a result of some chemical in the residual liquid (the residual of this sample was in liquid form) that reacted with the cotton piece and changed its characteristics. Therefore, the results of this medication should be used with caution.

Table 2. Summary of QA/QC checks for accuracy

Parameter	Measurement	QC Check	Method	Frequency	Acceptance Criteria	Accuracy Met?
Weight of residuals	Weight	Accuracy (bias)	Measure a standard weight	Once per day before conducting the measurements	± 0.1mg of the actual weight	Yes
Presence of active pharmaceutical ingredient in residuals	Temperature	Temperature calibration	1 point calibration	Initially (once at start of the project data collection) and as needed**	± 5 of the curie temperature of the standard metal	Yes
	Weight	Calibration Check	2 point calibration	Initially (once at start of the project data collection) and as needed	± 0.1 mg of the actual weight	Yes
		Accuracy (bias)	Measure a standard weight	Once per day before and after conducting the measurements	± 0.1 mg of the actual weight	Yes

** As needed: temperature calibration is needed when the temperature of the peak weight loss of the cotton piece is not in the range of 427 ± 5 °C.

The temperature calibrations of the TGA using Nickel standard are presented in Table 3.

Table 3. Temperature calibrations of the TGA

Date	Curie point of the Nickel standard (°C)	Actual measured Curie point (°C)	Acceptance Criteria	Comment
05/20/2013	358.28	358.43	± 5 of the curie temperature of the standard	Accepted
05/29/2013		355.65		Accepted
08/10/2013		359.56		Accepted

The temperature at which the maximum weight loss occurs was used to qualitatively evaluate the presence of the active pharmaceutical compounds in the residuals. This was achieved through comparing the temperature at which the maximum weight loss occurs for the pure pharmaceutical compounds (Table 4) to that of the residuals.

Table 4. Temperature for maximum weight loss for pure pharmaceutical compounds

Pure Compound	CAS #	Temperature for maximum weight loss on TGA (ºC)	Acceptance Criteria (ºC)
Warfarin Sodium	129-06-6	313	±5
Physostigmine Salicylate	57-64-7	236	±5
Nicotine	54-11-5	217	±5

6.2 Representativeness

Representativeness is the extent to which measurements actually depict the true condition or population being evaluated. The measurement of the residuals in the pharmaceutical containers was conducted using the container as a whole and not on portions of it. This ensures a high representativeness of the measurement. With regards to the TGA analysis on the residuals, a cotton piece was used to swab all the internal walls of the containers in order to ensure the representativeness of the measurement for the actual residuals in the containers.

6.3 Completeness

Completeness is number of data points meeting all data quality objectives (DQO)/total number data points. A completeness of 90 % is required for this project. The completeness (C) was calculated as follows and the results are presented in Table 3:

$$\%C = \frac{v}{T} \times 100$$

Where: v = the number of data points meeting DQO

T= the number of data points

Table 5. Completeness of the measurements

Measurement Parameter	Number of data points meeting DQO	Number of data points	Completeness (%C)	Acceptance criteria (90%)
Weight of residuals	153	153*	100%	Accepted
Temperature for maximum weight loss	150	153**	98%	Accepted

* 17 medications experimentally tested x 3 treatments (triple rinsed with DI, cleaned with methanol, cleaned with another organic solvent) x 3 (triplicate) = 153
** 17 medications experimentally tested x 3 treatments (not rinsed, triple rinsed with DI, cleaned with methanol) x 3 (triplicate) = 153. The TGA tests that failed the DQO were the triplicate nicotine nasal spray 10 mg/ml samples.

6.4 Comparability

Comparability is the extent to which data from one study can be compared to past data from the current project or data from another study. Data comparability was maintained through the use of defined and consistent sampling and analytical procedures. The standard operating procedures (SOPs) defined in the study QAPP were systematically followed each time a sample was being processed.

7 Conclusions

The current study aimed at evaluating if removing the P-listed drugs of warfarin sodium, nicotine, and physostigmine salicylate from their containers is equivalent to triple rinsing the containers. The study was conducted using thermal gravimetric analysis and weight measurements using a microbalance. The TGA was used to qualitatively evaluate the presence of the active pharmaceutical ingredient in the residuals after removing the drug from the rinsed pharmaceutical containers by comparing the $T_{max\ wt\ loss}$ of the residuals to that of the pure active pharmaceutical compound. The total amount of residuals in pharmaceutical containers containing warfarin, physostigmine salicylate and nicotine medications after removing the drugs were measured using a microbalance. The theoretical "maximum possible weight of residual drug/total residual /container" was calculated for each compound and packaging combination. This calculated result may be used to infer an upper limit for the amount of pharmaceutical compound in the total residue remaining in the container. A total of 18 drug/packaging combinations were evaluated in the study. The results obtained in the study are summarized in Table 6, and indicate the following:

- For the medications in liquid form (Nicotrol nasal spray 10 mg/ml and Physostigmine salicylate 1 mg/ml), there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not triple-rinsed containers contain the active pharmaceutical ingredient. It should be noted that the tested liquid medications were solutions (not suspensions) and there was no mention of a requirement or recommendation to shake the medication before use on the drug package.
- For Nicotine inhaler 10 mg/cartridges, there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not-triple-rinsed containers contain the active pharmaceutical ingredient. The amount of nicotine in the residue was not calculated based on experimental results; rather, it was calculated based on information provided by the manufacturer. On the package, it was stated that every cartridge contained 10 mg nicotine and only 4 mg out of the 10 mg will be delivered, and thus, 6 mg nicotine will be retained in each used cartridge.
- For the medications in solid form (i.e., tablet, gum, and lozenge) and patches, the TGA results showed no difference between triple-rinsed containers and those that are not triple-rinsed. However, this conclusion is based on a qualitative analysis by TGA that is limited by the TGA sensitivity. Other analytical techniques (e.g., gas chromatography or liquid chromatography equipped with mass spectrometer) are needed to verify the TGA results for these medications and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any).

The above conclusions present the straight answer to the main research question of the study which was "Is there a difference between triple-rinsed P-listed pharmaceutical containers and those that are not triple-rinsed?" Additional conclusions are presented below and highlight other findings obtained herein as well as limitations of the analysis:

- The medications packaged in blister packs and plastic wraps contained minimal residuals, in the range of the error of the balance used in the study, after removing the drugs. Although the sensitivity of the balance did not allow for determining the actual amount of total residues in these package types, the results infer an upper limit for the total amount of residues in these packages.
- All medications packaged in plastic containers contained measurable amount of residuals (using balance data) after removing the drugs. An exception happened for two medications, Nicorette lozenges 2 mg and Nicorette lozenges 4 mg. Although residues were visually present in the empty

containers of these two medications and were detected by TGA, the amount of residues detected by the balance was within the range of the balance error. The balance results in this case were inconclusive.

- The theoretical "maximum possible weight of residual active compound/total residual /container" was calculated for each compound and packaging combination (Table 5). The calculated amounts may be used to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container.
- Any medication in liquid form must contain the active pharmaceutical ingredient in the residuals. This is because the active pharmaceutical ingredient is highly likely to be homogenously distributed in the liquid. Therefore, for any liquid medication, the actual amount of drug in the residuals can be calculated by knowing 1) the weight of residuals, and 2) the concentration of the active pharmaceutical ingredient in the medication as stated by the manufacturer. Despite this fact, the TGA results for physostigmine medication did not show the presence of the physostigmine compound in the residuals although the calculated amount of physostigmine in the residue in each ampule was 73 µg. The reason for the negative TGA results in this case could be explained by the limited capacity of the cotton piece to absorb all the amount of liquid residue in the empty ampule. This means that only a fraction of the total residue was loaded on the cotton piece, and thus, only a fraction of the 73 µg of physostigmine was available to be detected by the TGA. It should be noted that the majority of residue absorbed by the cotton piece was liquid water as indicated by the $T_{max\ wt\ loss}$ at 103 °C.
- The nicotine nasal spray 10 mg/ml was the only medication to have positive TGA results (active pharmaceutical drug was detected in the residuals) as the residues had a $T_{max\ wt\ loss}$ at 217 ^{o}C that is representative of nicotine. But the $T_{max\ wt\ loss}$ for the negative control (cotton piece) was shifted in this case, which may be attributed to a reaction between the residual liquid and the cotton piece that caused changes in the properties of the cotton piece. Nonetheless, the fact that this medication is in liquid from and contains 67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ^{o}C represents nicotine.
- For the blister packs and nicotine patches, the calculated upper limit for the amount of active pharmaceutical compound in the total residue was relatively low and ranged from 0 to 8 µg. These amounts are upper limits, and the actual amounts of active compounds in the residues are more than likely lower because the outer layer of the medication acts as a coating to prevent the loss of the drug until the medication reaches the target location in the body and thus, this layer does not probably contain the drug. The balance and upper limit results support the TGA results, which were negative for these pharmaceutical packages.
- For the plastic containers encompassing warfarin tablets (1, 5, and 10 mg), detectable quantities of residues were found in the empty containers. The TGA results for the same containers showed clear peaks for these residues; however, the peaks did not correspond to the warfarin and thus, they most likely represent the coating materials. These data support the aforementioned assumption that the residues in these cases are mainly composed of coating materials. Nonetheless, having negative TGA results do not eliminate the possibility of the presence of the active pharmaceutical compound in the residues. However, if it is present, it represents a relatively small fraction.
- Conclusions 5, 6, and 7 highlight the importance of considering the balance results and TGA results collectively rather than individually when analyzing the data.

Table 6. Summary of the results and limitations of analysis

Medication	Dose	Package Type	TGA Results				Total weight of residues		Calculated Upper Limit for Amount of Active Pharmaceutical Ingredient (µg)
			$T_{max\ wt\ loss}$ for Residues	$T_{max\ wt\ loss}$ for Pure Compound	Results	Limitation of Analysis	Weight (mg)	Limitation of Analysis	
Warfarin	Warfarin sodium tablets, 1 mg	Plastic container	245 ºC	313 ºC	Negative	Qualitative	19.8	NA	90
	Warfarin sodium tablets, 5 mg	Plastic container	239 ºC	313 ºC	Negative	Qualitative	17.5	NA	390
	Warfarin sodium tablets, 10 mg	Plastic container	231 ºC	313 ºC	Negative	Qualitative	19.8	NA	890
	Warfarin sodium tablets, 2 mg	Blister pack	None	313 ºC	Negative	Qualitative	0.3	Within range of error	3
	Jantoven tablets, 1 mg	Blister pack	None	313 ºC	Negative	Qualitative	0.3	Within range of error	1
	Jantoven tablets, 10 mg	Blister pack	None	313 ºC	Negative	Qualitative	0.2	Within range of error	8
Nicotine	Nicorette gum, 2 mg	Blister pack	None	217 ºC	Negative	Qualitative	0.3	Within range of error	0.5
	Nicorette gum, 4 mg	Blister pack	None	217 ºC	Negative	Qualitative	0.3	Within range of error	0.8
	Nicotine polacrilex gum, 2 mg	Blister pack	None	217 ºC	Negative	Qualitative	0.1	Within range of error	0.2
	Nicotine polacrilex gum, 4 mg	Blister pack	None	217 ºC	Negative	Qualitative	0.1	Within range of error	0.3

Table 6. Summary of the results and limitations of analysis (Cont'd)

Medication	Dose	Package Type	TGA Results				Total weight of residues		Calculated Upper Limit for Amount of Active Pharmaceutical Ingredient (µg)
			$T_{max\ wt\ loss}$ for Residues	$T_{max\ wt\ loss}$ for Pure Compound	Results	Limitation of Analysis	Weight (mg)	Limitation of Analysis	
Nicotine	Nicorette mini lozenge, 2 mg	Plastic container	306 °C	217 °C	Negative	Qualitative	0.2	Uncertainty of measurement [a]	NA
	Nicorette lozenge, 4 mg	Plastic container	324 °C	217 °C	Negative	Qualitative	0.0	Uncertainty of measurement [a]	NA
	Nicotine transdermal patch, 7 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.1	Within range of error	1.0
	Nicotine transdermal patch, 14 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.0	Within range of error	0.0
	Nicotine transdermal patch, 21 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.0	Within range of error	0.0
	Nicotrol nasal spray, 10 mg/ml	Glass vial	217 °C	217 °C	Positive	Uncertainty with the negative control	67.8	NA	67.8
	Nicotine inhaler, 10 mg/cartridge	Plastic container	NA	NA	NA	Qualitative	NA	NA	6000 [b]
Physostig-mine salicylate	Physostig-mine salicylate, 1 mg/ml	Glass ampule	103 °C	236 °C	Negative	Qualitative	73	NA	73

[a] Although residues were visually present in the empty container and were detected by TGA, the amount of residues detected by the balance was within the range of the balance error. The balance results in this case were inconclusive. [b] This value was not calculated based on experimental results, rather it was calculated based on information provided by the manufacturer. On the package, it was stated that every cartridge contain 10 mg nicotine and only 4 mg out of the 10 mg will be delivered when used.

8 Appendix A

Appendix A

Summary of the Residual Weight Results and Calculations

Table A-1: Warfarin Sodium Tablets 1mg (Item # 830-612), plastic bottles

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (gm) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	9.6249	9.6110	Not Applicable	0.0139	0.0152	0.0012
	9.5810	9.5654		0.0156		
	9.4592	9.4430		0.0162		
Cleaned with methanol (negative control)	9.5256	9.5105	9.5048	0.0208	0.0198*	0.0009**
	9.5666	9.5526	9.5473	0.0193		
	9.4594	9.4455	9.4401	0.0193		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue

** Stdev of residuals (S)

Table A-2: Calculated upper limit for the amount of active ingredient warfarin sodium in container residue (Warfarin Sodium Tablets 1mg)

Weight of randomly selected tablets(gm)	**Average weight (g)**	**Stdev weight (g)**	**% drug/Tablet**	**Number of tablets/Container**	**Total weight of all tablets (g)**	**Weight of drug/Container (g)**	****Maximum possible weight of residual drug/Total residual/container (mg)**	**Stdev**
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2180	0.2199	0.0029	0.4547	100	21.9920	0.1000	0.0900	0.0039
0.2244								
0.2184								
0.2213								
0.2175								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

Table A-3: Warfarin Sodium Tablets 5mg (Item # 824-896), plastic bottles

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	9.4004	9.3888	Not Applicable	0.0116	0.0153	0.0033
	9.4616	9.4455		0.0161		
	9.5951	9.5770		0.0181		
Cleaned with methanol (negative control)	9.4118	9.3932	9.3933	0.0185	0.0175*	0.0011**
	9.5228	9.5053	9.5052	0.0176		
	9.4059	9.3897	9.3896	0.0163		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-4: Calculated upper limit for the amount of warfarin sodium in empty container residue (Warfarin Sodium Tablets 5mg)

Weight of randomly selected tablets (g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2278	0.2247	0.0023	2.2254	100	22.4680	0.5000	0.3887	0.0246
0.2235								
0.2260								
0.2243								
0.2218								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

Table A-5: Warfarin Sodium Tablets 10mg (Item # 822-965), plastic bottles

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	9.3765	9.3622	Not Applicable	0.0143	0.0157	0.0025
	9.4651	9.4509		0.0142		
	9.4116	9.3931		0.0185		
Cleaned with methanol (negative control)	9.4285	9.4121	9.4073	0.0212	0.0198*	0.0012**
	9.3187	9.3047	9.2998	0.0189		
	9.6159	9.6014	9.5965	0.0194		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-6: Calculated upper limit for the amount of warfarin sodium in empty container residue (Warfarin Sodium Tablets 10 mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2227	0.2230	0.0015	4.4847	100	22.2980	1.0000	0.8895	0.0543
0.2234								
0.2253								
0.2214								
0.2221								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

Table A-7: Warfarin Sodium 2mg (Item # 580-516), blister packs

Treatment	**##Weight before treatment (g)**	**## Weight after first triple rinse (g)**	**## Weight after second triple rinse (g)**	**Weight of residuals (g)**	**Average weight of residuals (gm) (W)**	**Stdev weight of residuals (gm) (S)**
Triple rinse with DI water	3.5586	3.5559	Not Applicable	0.0003	0.0002	0.0001
	3.5459	3.5433		0.0003		
	3.5101	3.5085		0.0002		
Cleaned with methanol (negative control)	3.5285	3.5257	3.5256	0.0003	0.0003*	0.0000**
	3.5108	3.5082	3.5079	0.0003		
	3.5386	3.5364	3.5361	0.0003		

Weight of the whole empty card which contains 10 individual blister packs. Thus the weight of residuals was calculated as the difference between the weights before and after rinse divided by 10. This measurement has been conducted this way because the amount of residuals in individual packs is too small to be detected by the utilized balance.

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-8: Calculated upper limit for the amount of warfarin sodium in empty container residue (Warfarin Sodium 2 mg)

Weight of randomly selected tablets(g)	**Average weight (g)**	**Stdev weight (g)**	**% drug/Tablet**	**Number of tablets/Container**	**Total weight of tablets (g)**	**Weight of drug/Container (g)**	****Maximum possible weight of residual drug/Total residual/container (mg)**	**Stdev**
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2168	0.2170	0.0023	0.9217	1	0.2170	0.0020	0.0026	0.0002
0.2202								
0.2181								
0.2147								
0.2151								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body.

Table A-9: Jantoven (Warfarin Sodium) 1mg (Item # 015-920), blister packs

Treatment	##Weight before treatment (g)	## Weight after first triple rinse (g)	## Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	3.0942	3.0918	Not Applicable	0.0002	0.0002	0.0000
	3.1217	3.1195		0.0002		
	3.0691	3.0668		0.0002		
Cleaned with methanol (negative control)	3.0748	3.0721	3.0721	0.0003	0.0003*	0.0000**
	3.0626	3.0602	3.0602	0.0002		
	3.0526	3.0497	3.0497	0.0003		

Weight of the whole empty card which contains 10 individual blister packs. Thus the weight of residuals was calculated as the difference between the weights before and after rinse divided by 10. This measurement has been conducted this way because the amount of residuals in individual packs is too small to be detected by the utilized balance.

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-10: Calculated upper limit for the amount of warfarin sodium in empty container residue (Jantoven 1 mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2226	0.2243	0.0027	0.4459	1	0.2243	0.0010	0.0012	0.0001
0.2224								
0.2223								
0.2257								
0.2283								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-11: Jantoven (Warfarin Sodium) 10mg (Item # 014-528), blister packs

Treatment	**##Weight before treatment (g)**	**## Weight after first rinse (g)**	**## Weight after second rinse (g)**	**Weight of residuals (g)**	**Average weight of residuals (gm) (W)**	**Stdev weight of residuals (g) (S)**
Triple rinse with DI water	3.0737	3.0714	Not Applicable	0.0002	0.0002	0.0000
	3.0453	3.0434		0.0002		
	3.0268	3.0250		0.0002		
Cleaned with methanol (negative control)	3.0484	3.0464	3.0464	0.0002	0.0002*	0.0000**
	3.0589	3.0569	3.0569	0.0002		
	3.0465	3.0448	3.0448	0.0002		

Weight of the whole empty card which contains 10 individual blister packs. Thus the weight of residuals was calculated as the difference between the weights before and after rinse divided by 10. This measurement has been conducted this way because the amount of residuals in individual packs is too small to be detected by the utilized balance.

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-12: Calculated upper limit for the amount of warfarin sodium in empty container residue (Jantoven 10 mg)

Weight of randomly selected tablets(g)	**Average weight (g)**	**Stdev weight (g)**	**% drug/Tablet**	**Number of tablets/Container**	**Total weight of tablets (g)**	**Weight of drug/Container (g)**	****Maximum possible weight of residual drug/Total residual/container (mg)**	**Stdev**
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.2255	0.2252	0.0010	4.4397	1	0.2252	0.0100	0.0084	0.0008
0.2238								
0.2265								
0.2249								
0.2255								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-13: Nicorette Gum (fruit Chill) 2mg (Item #151579), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (gm) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.2531	0.2529	Not Applicable	0.0002	0.0002	0.0001
	0.2427	0.2424		0.0003		
	0.2501	0.2499		0.0002		
Cleaned with methanol (negative control)	0.2433	0.2430	Not Applicable	0.0003	0.0003*	0.0002**
	0.2536	0.2534		0.0002		
	0.2569	0.2564		0.0005		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-14: Calculated upper limit for the amount of nicotine in empty container residue (Nicorette Gum (fruit Chill) 2mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
1.2842	1.2864	0.0103	0.1555	1	1.2864	0.0021	0.0005	0.0002
1.2976								
1.2920								
1.2702								
1.2878								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-15: Nicorette Gum (fruit Chill) 4mg (Item #151542), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.2661	0.2660	Not Applicable	0.0001	0.0002	0.0001
	0.2695	0.2692		0.0003		
	0.2501	0.2500		0.0001		
Cleaned with methanol (negative control)	0.2482	0.2479	Not Applicable	0.0003	0.0003*	0.0001**
	0.2571	0.2569		0.0002		
	0.2521	0.2518		0.0003		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-16: Calculated upper limit for the amount of nicotine in empty container residue (Nicorette Gum (fruit Chill) 4mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
1.2831	1.2830	0.0307	0.3118	1	1.2830	0.0040	0.0008	0.0002
1.3006								
1.2822								
1.3152								
1.2337								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug, rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-17: Nicotine Gum Polacrilex 2mg (Item #753-121), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (gm)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.2444	0.2442	Not Applicable	0.0002	0.0001	0.0001
	0.2577	0.2576		0.0001		
	0.2533	0.2533		0.0000		
Cleaned with methanol (negative control)	0.2584	0.2582	Not Applicable	0.0002	0.0001*	0.0001**
	0.2566	0.2565		0.0001		
	0.2605	0.2605		0.0000		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-18: Calculated upper limit for the amount of nicotine in empty container residue (Nicotine Gum Polacrilex 2mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.9546	0.9650	0.0085	0.2072	1	0.9650	0.0020	0.0002	0.0002
0.9663								
0.9777								
0.9658								
0.9607								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-19: Nicotine Gum Polacrilex 4mg (Item #753-133), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (gm) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.2511	0.2511	Not Applicable	0.0000	0.0001	0.0001
	0.2556	0.2555		0.0001		
	0.2520	0.2519		0.0001		
Cleaned with methanol (negative control)	0.2543	0.2542	Not Applicable	0.0001	0.0001	0.0001
	0.2554	0.2554		0.0000		
	0.2651	0.2650		0.0001		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-20: Calculated upper limit for the amount of nicotine in empty container residue (Nicotine Gum Polacrilex 4mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.9748	0.9579	0.0172	0.4176	1	0.9579	0.0040	0.0003	0.0002
0.9648								
0.9574								
0.9633								
0.9292								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-21: Nicorette mini Lozenges 2mg (Item #030256), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	#Weight of residuals (g)	Average weight of residuals (g)
Triple rinse with DI water	12.8935	12.8934	Not Applicable	0.0001	0.0000
	12.8906	12.8906		0.0000	
	**	**	**	**	
Cleaned with methanol (negative control)	13.0467	13.0463	Not Applicable	0.0004	0.0002
	12.9654	12.9654		0.0000	
	**	**	**		

It is noted that residuals could be visually seen in the empty containers after disposing of the lozenges. But the weight is negligible as compared to the relatively large container weight. So the residuals were not detectable by the balance. But these residuals were detected by the TGA.

** Only duplicate samples were tested

Table A-22: Nicorette Lozenges 4mg (Item #002-089), blister packs

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	#Weight of residuals (g)	Average weight of residuals (g)	Stdev weight of residuals (g)
Triple rinse with DI water	28.0900	28.0900	Not Applicable	0.0000	0.0000	0.0001
	27.8721	27.8720		0.0001		
	28.1864	28.1864		0.0000		
Cleaned with methanol (negative control)	27.8877	27.8877	Not Applicable	0.0000	0.0000	0.0000
	27.8521	27.8521		0.0000		
	27.8813	27.8813		0.0000		

It is noted that residuals could be visually seen in the empty containers after disposing of the lozenges. But the weight is negligible as compared to the relatively large container weight. So the residuals were not detectable by the balance. But these residuals were detected by the TGA

** Only duplicate samples were tested

Table A-23: Nicotine Transdermal Patch 7mg (Item #414-944), patch (plastic wrap to peel)

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.1041	0.1040	Not Applicable	0.0001	0.0000	0.0001
	0.1038	0.1038		0.0000		
	0.1040	0.1040		0.0000		
Cleaned with methanol (negative control)	0.1046	0.1044	Not Applicable	0.0002	0.0001*	0.0002**
	0.1052	0.1051		0.0001		
	0.1043	0.1044		-0.0001		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-24: Calculated upper limit for the amount of nicotine in empty container residue (Nicotine Transdermal Patch 7mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
0.4146	0.4142	0.0006	1.6899	1	0.4142	0.0070	0.0011	0.0026
0.4145								
0.4137								
0.4148								
0.4135								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-25: Nicotine Transdermal Patch 14mg (Item #722-285), patch (plastic wrap to peel)

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.5232	0.5232	Not Applicable	0.0000	0.0000	0.0000
	0.5289	0.5289		0.0000		
	0.5461	0.5461		0.0000		
Cleaned with methanol (negative control)	0.5134	0.5134	Not Applicable	0.0000	0.0000*	0.0000**
	0.5384	0.5384		0.0000		
	0.5385	0.5385		0.0000		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-26: Calculated upper limit for the amount of nicotine in empty container residue (Nicotine Transdermal Patch 14mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
1.3442	1.3476	0.0024	1.0389	1	1.3476	0.0140	0.0000	0.000
1.3486								
1.3465								
1.3506								
1.3479								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug; rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-27: Nicotine Transdermal Patch 21mg (Item #414-969), patch (plastic wrap to peel)

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g) (W)	Stdev weight of residuals (g) (S)
Triple rinse with DI water	0.3020	0.3019	Not Applicable	0.0001	0.0000	0.0001
	0.3015	0.3015		0.0000		
	0.2987	0.2987		0.0000		
Cleaned with methanol (negative control)	0.2989	0.2989	Not Applicable	0.0000	0.0000*	0.0001**
	0.3050	0.3050		0.0000		
	0.3054	0.3053		0.0001		

*Average weight of residuals (W) used in the calculations of the upper limit for the amount of active ingredient in container residue, ** Stdev. of residuals (S)

Table A-28: Calculated upper limit for the amount of nicotine in empty container residue (Nicotine Transdermal Patch 21mg)

Weight of randomly selected tablets(g)	Average weight (g)	Stdev weight (g)	% drug/Tablet	Number of tablets/Container	Total weight of tablets (g)	Weight of drug/Container (g)	**Maximum possible weight of residual drug/Total residual/container (mg)	Stdev
A	B	C	D	E	F	G	H	I
			As per manufacturer		F=B*E	G=D*F	H=W*(D/100)	I=(S/1000)*(D/100)
1.2216	1.2259	0.0024	1.7130	1	1.2259	0.0210	0.0000	0.0010
1.2275								
1.2264								
1.2272								
1.2269								

** Assuming that the drug is homogenously distributed so it will have the same concentration in the residual as in the medication. This assumption represents the worst case scenario. In reality, the outer layer of the medication does not probably contain the drug, rather it may be a coating to prevent the loss of the drug until the medication reaches the location where it should be delivered in the body

Table A-29: Nicotrol NS Nasal Spray 10 mg/ml (Item # 500948), glass vial

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g)	# Stdev weight of residuals (g)
Triple rinse with DI water	11.1850	11.1489	Not Applicable	0.0361	0.0472	0.0215
	11.2278	11.1558		0.0720		
	11.1780	11.1444		0.0336		
Cleaned with methanol (negative control)	11.0927	11.0469	11.0469	0.0458	0.0678	0.0369
	11.1898	11.0795	11.0794	0.1104		
	11.3298	11.2826	11.2826	0.0472		

The high standard deviation in this case is a result of the nature of the medication. The medication is in liquid form and therefore, when removing the medication from the container, the remaining liquid is expected to have significant differences from one container to the other when emptying the container when trying to simulate the use.

Volume of liquid per vial 10 ml

Nicotine Concentration in the vial 10 mg/ml

Total nicotine per vial 100 mg

Average total amount of residual nicotine per vial 0.6780 mg

Stdev of the total amount of residual nicotine per vial 0.3690 mg

Table A-30: Physostigmine Salicylate Ampules 1mg/ml (Item # 003-012), glass ampule

Treatment	Weight before treatment (g)	Weight after first triple rinse (g)	Weight after second triple rinse (g)	Weight of residuals (g)	Average weight of residuals (g)	Stdev weight of residuals (g)
Triple rinse with DI water	1.8730	1.8499	Not Applicable	0.0231	0.0651	0.0398
	1.9563	1.8862		0.0701		
	1.9636	1.8614		0.1022		
Cleaned with methanol (negative control)	1.9289	1.8497	1.8492	0.0797	0.0730	0.0220
	1.9280	1.8796	1.8796	0.0484		
	1.9602	1.8700	1.8694	0.0908		

Drug concentration is 1 mg/ml

Volume of drug /ampule is 2 ml

Total weight of drug/ampule is 2mg

Average actual residual drug/ampule is 0.0730 mg

Stdev of actual residual drug/ampule is 0.0220 mg

9 Appendix B

Appendix B

Overlay of TGA Plots for the Treatments of Each Medication Containers

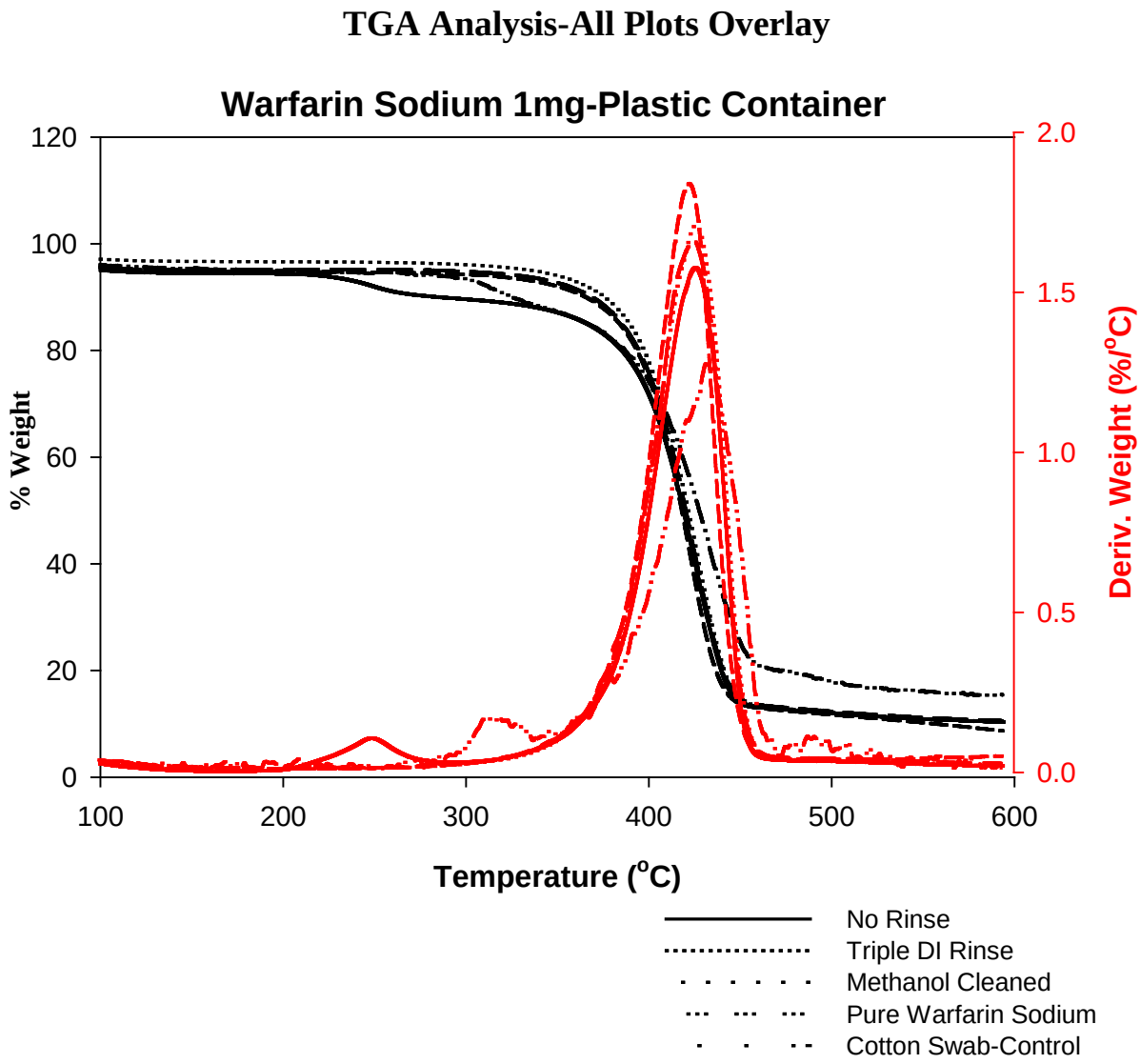


Figure B-1: Warfarin Sodium 1 mg, plastic container

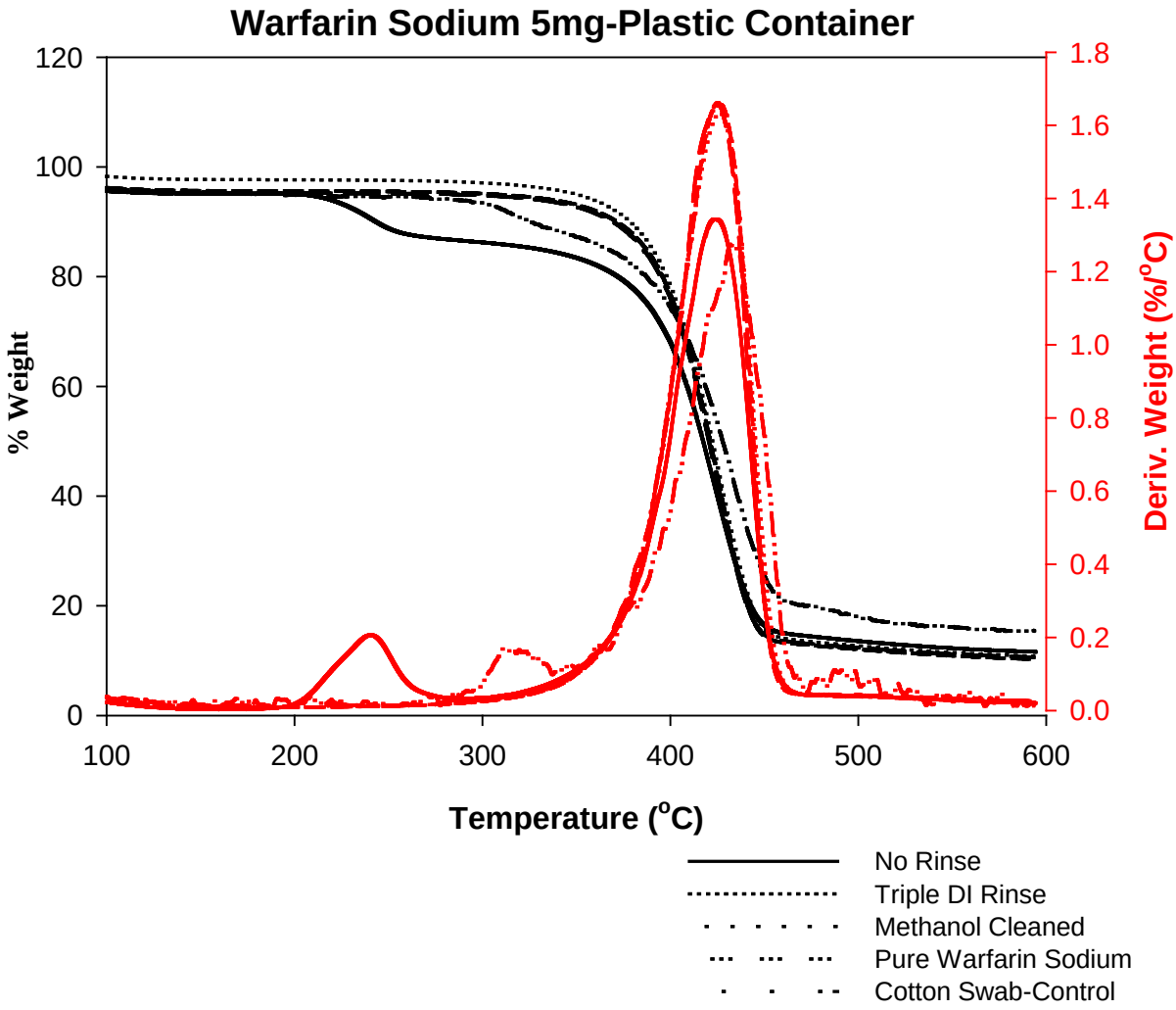


Figure B-2: Warfarin Sodium 5 mg, plastic container

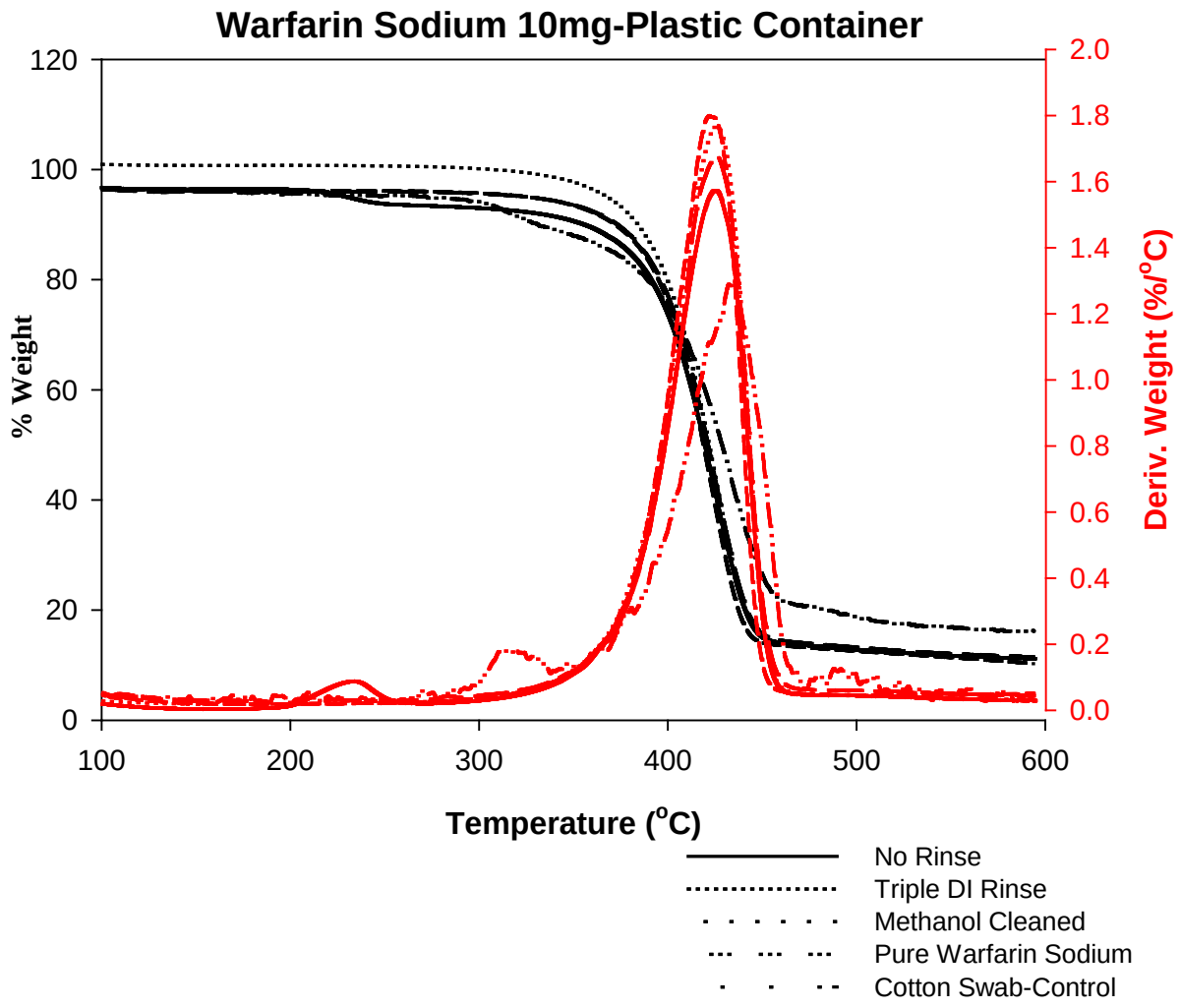


Figure B-3: Warfarin Sodium 10 mg, plastic container

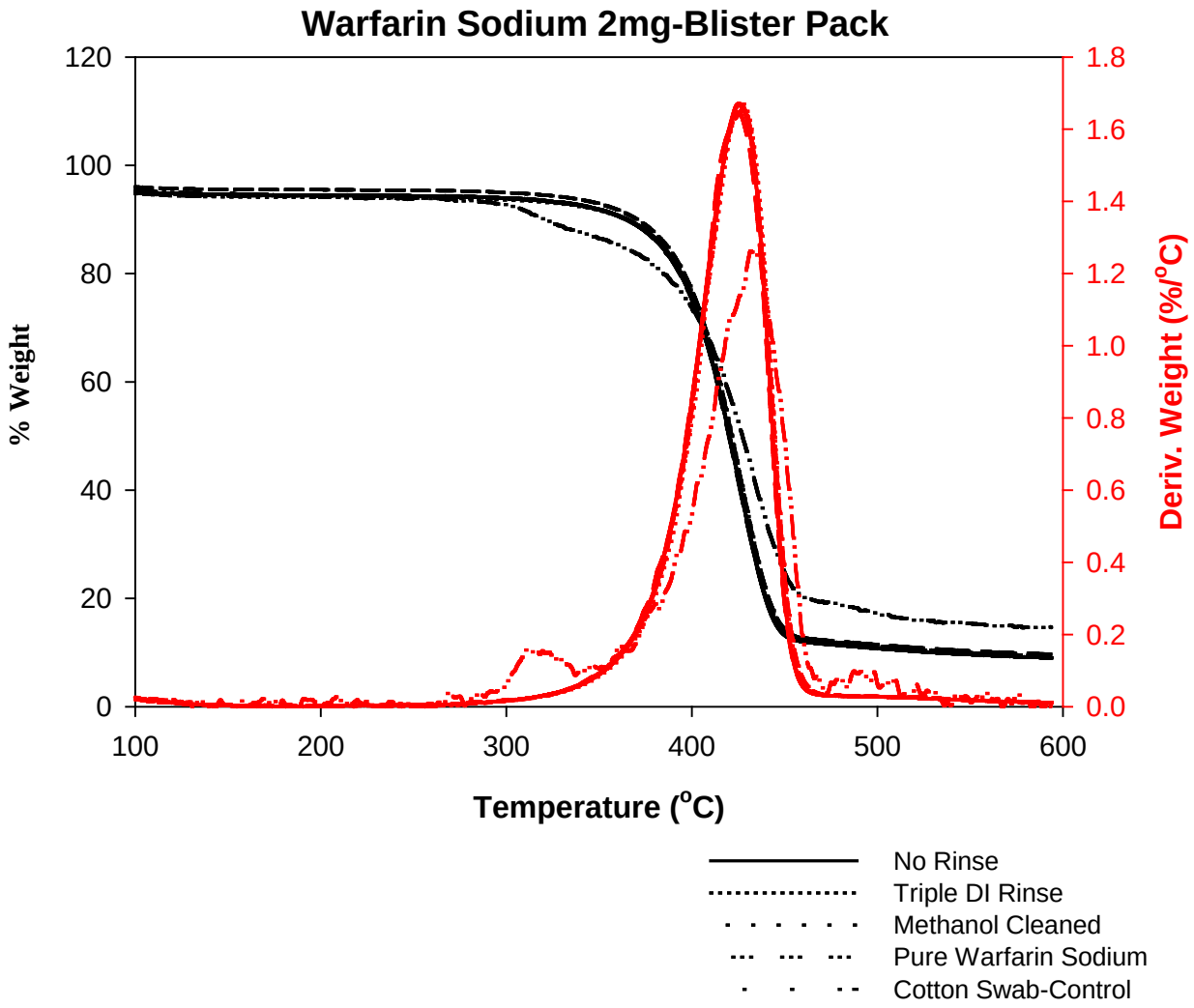


Figure B-4: Warfarin Sodium 2 mg, blister packs

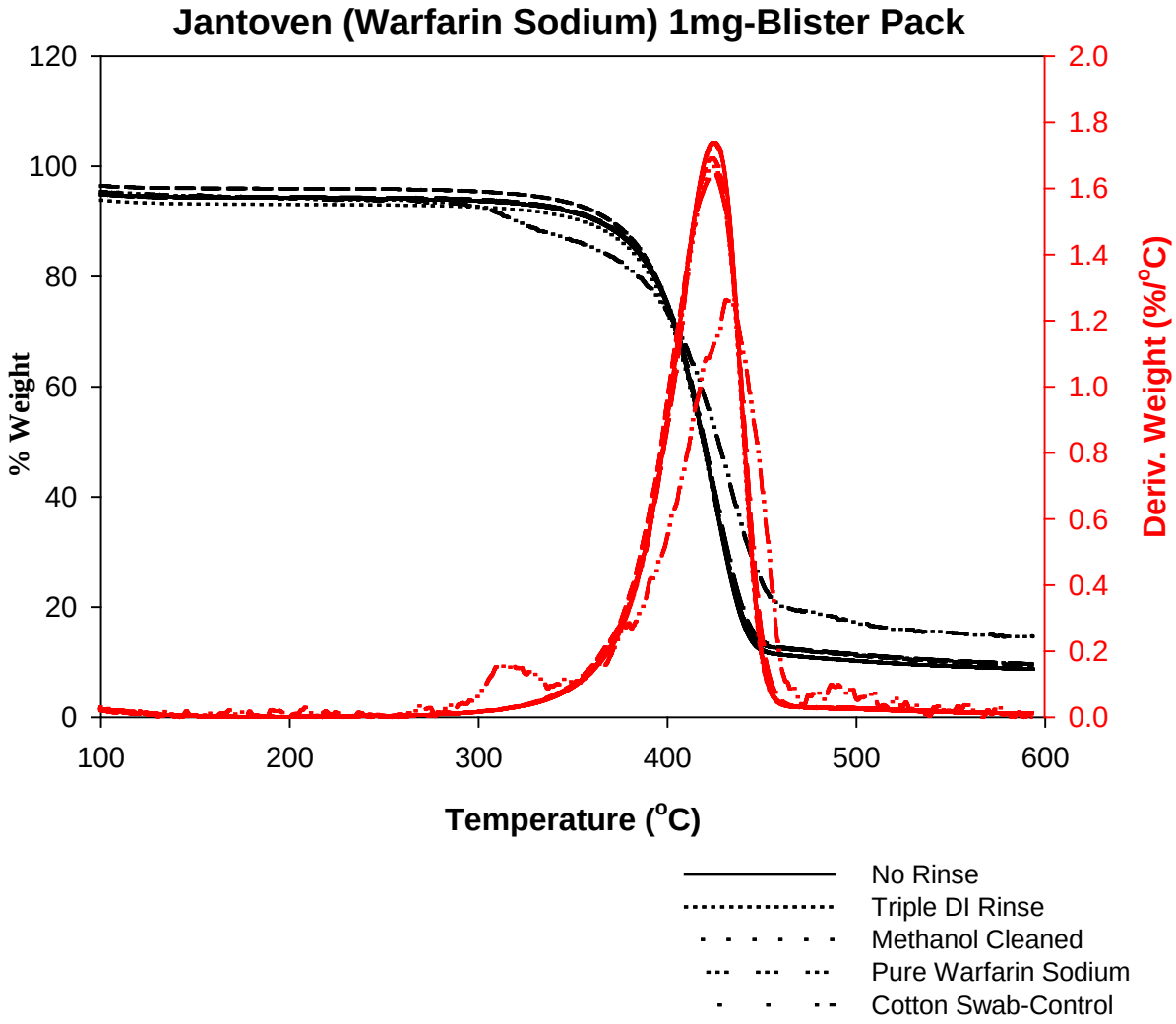


Figure B-5: Jantoven (Warfarin Sodium) 1 mg, blister packs

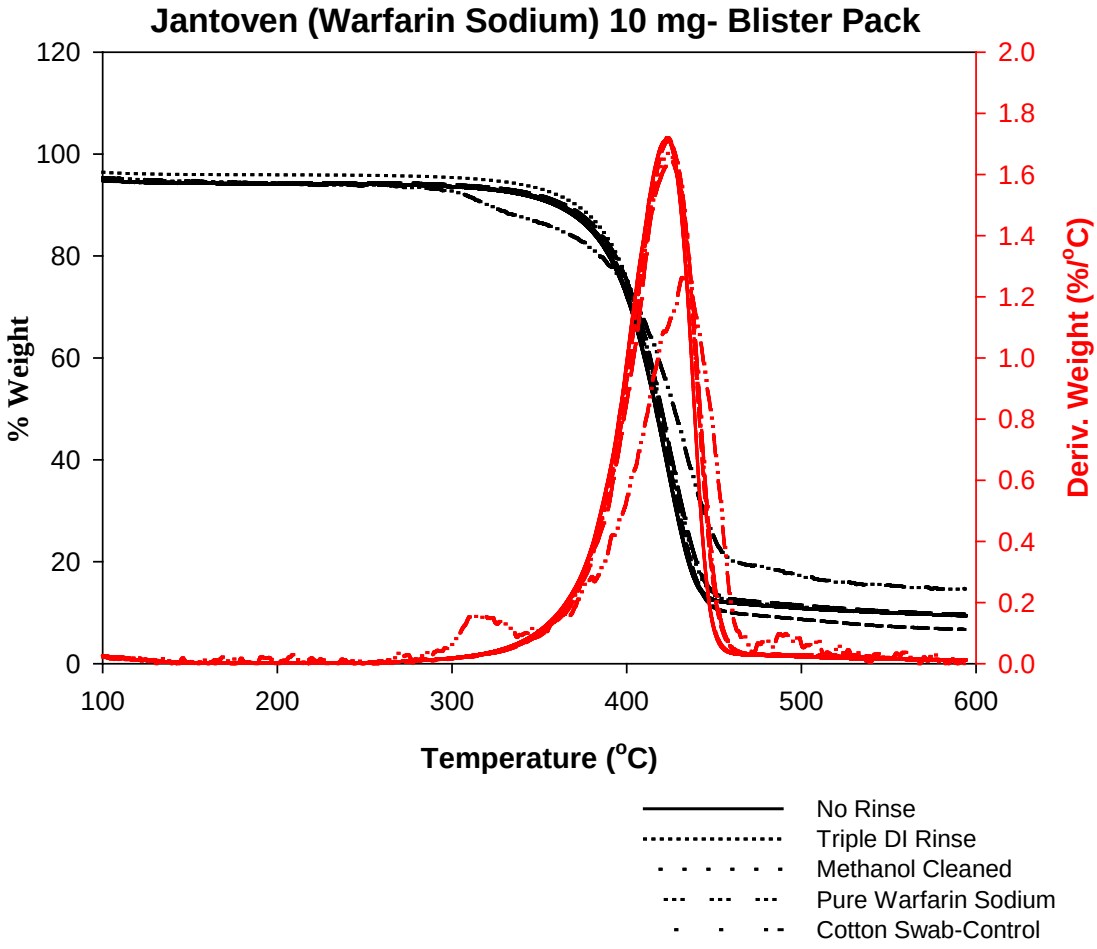


Figure B-6: Jantoven (Warfarin Sodium) 10 mg, blister packs

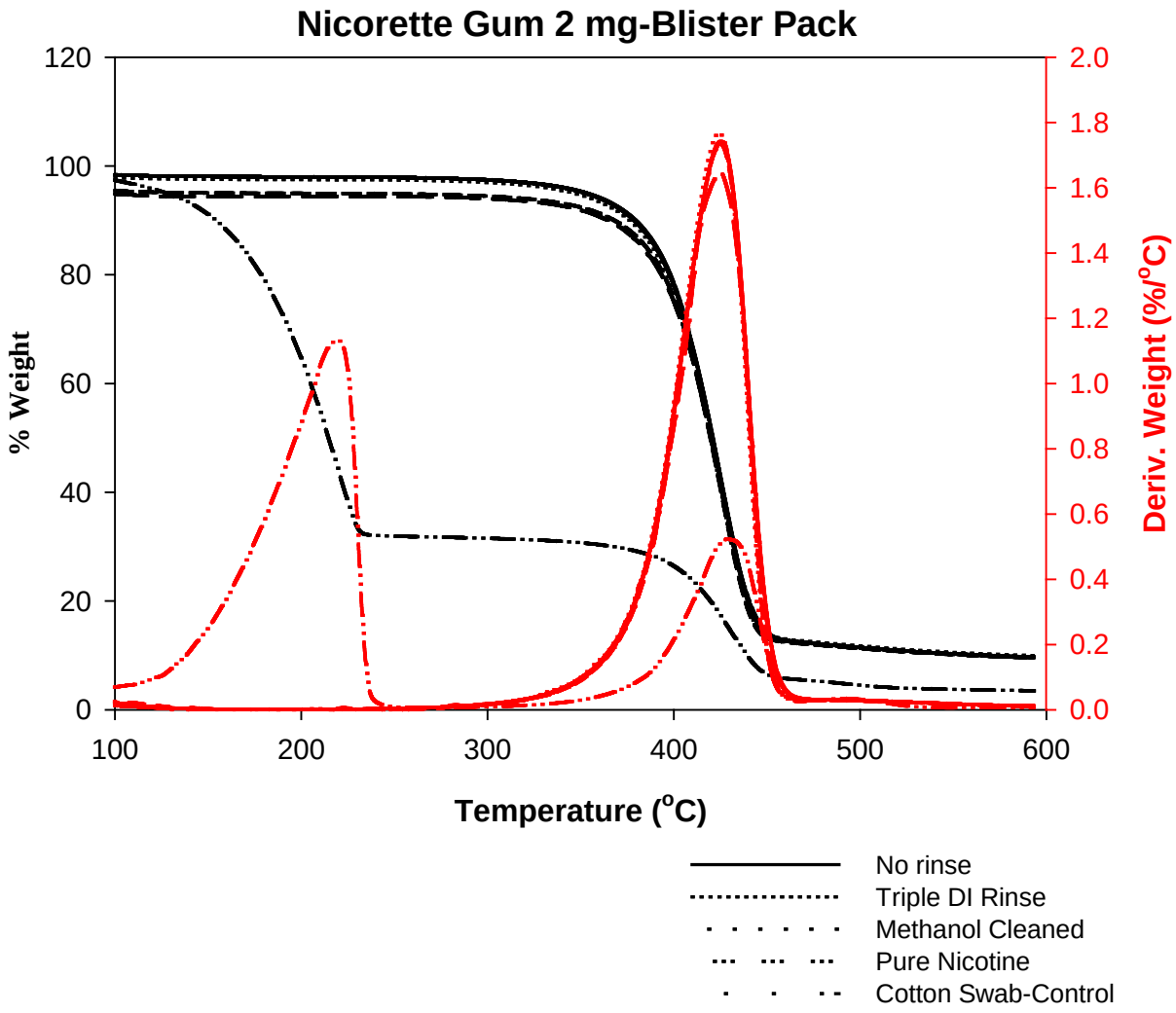


Figure B-7: Nicorette gum 2 mg, blister packs

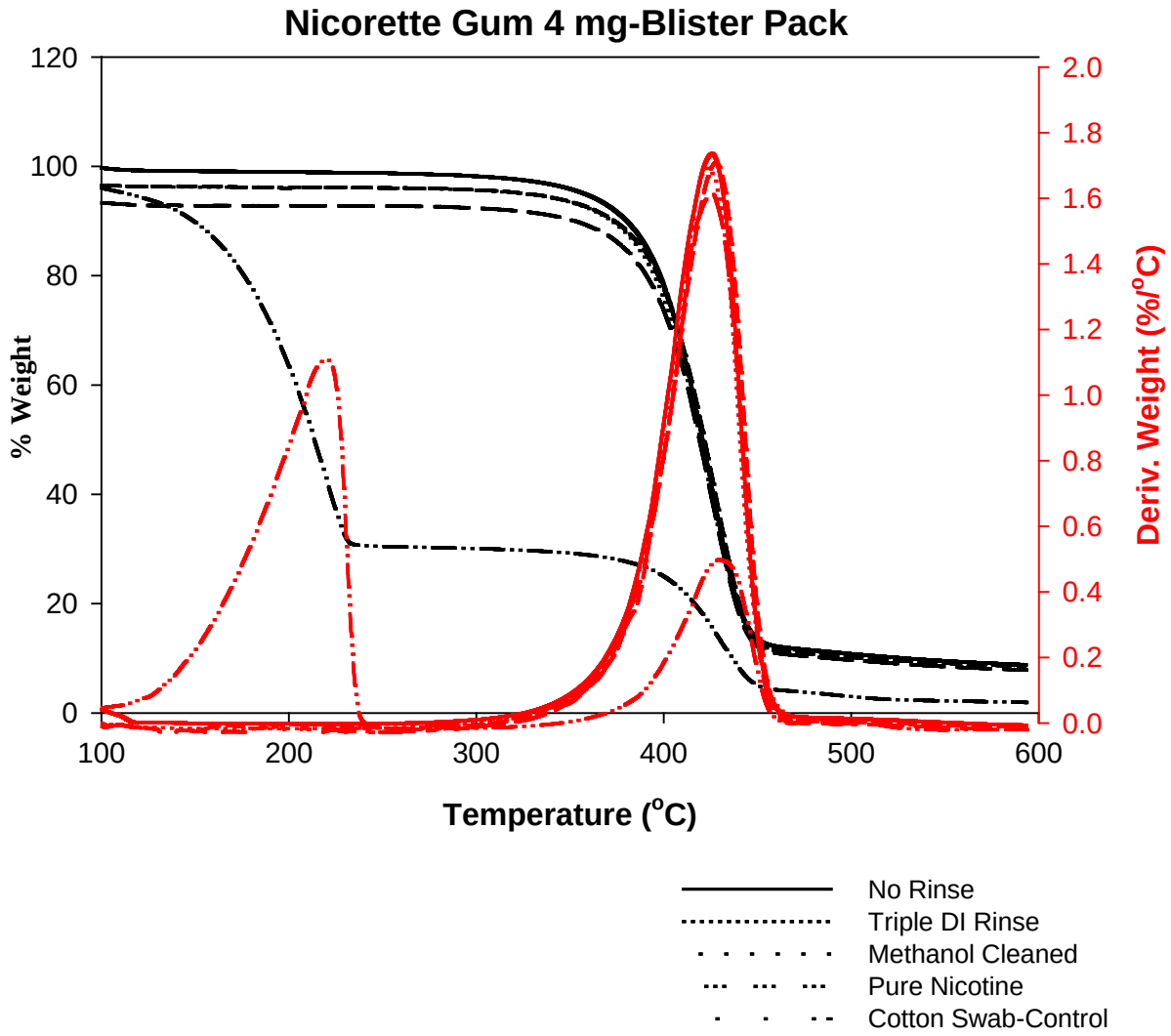


Figure B-8: Nicorette gum 4 mg, blister packs

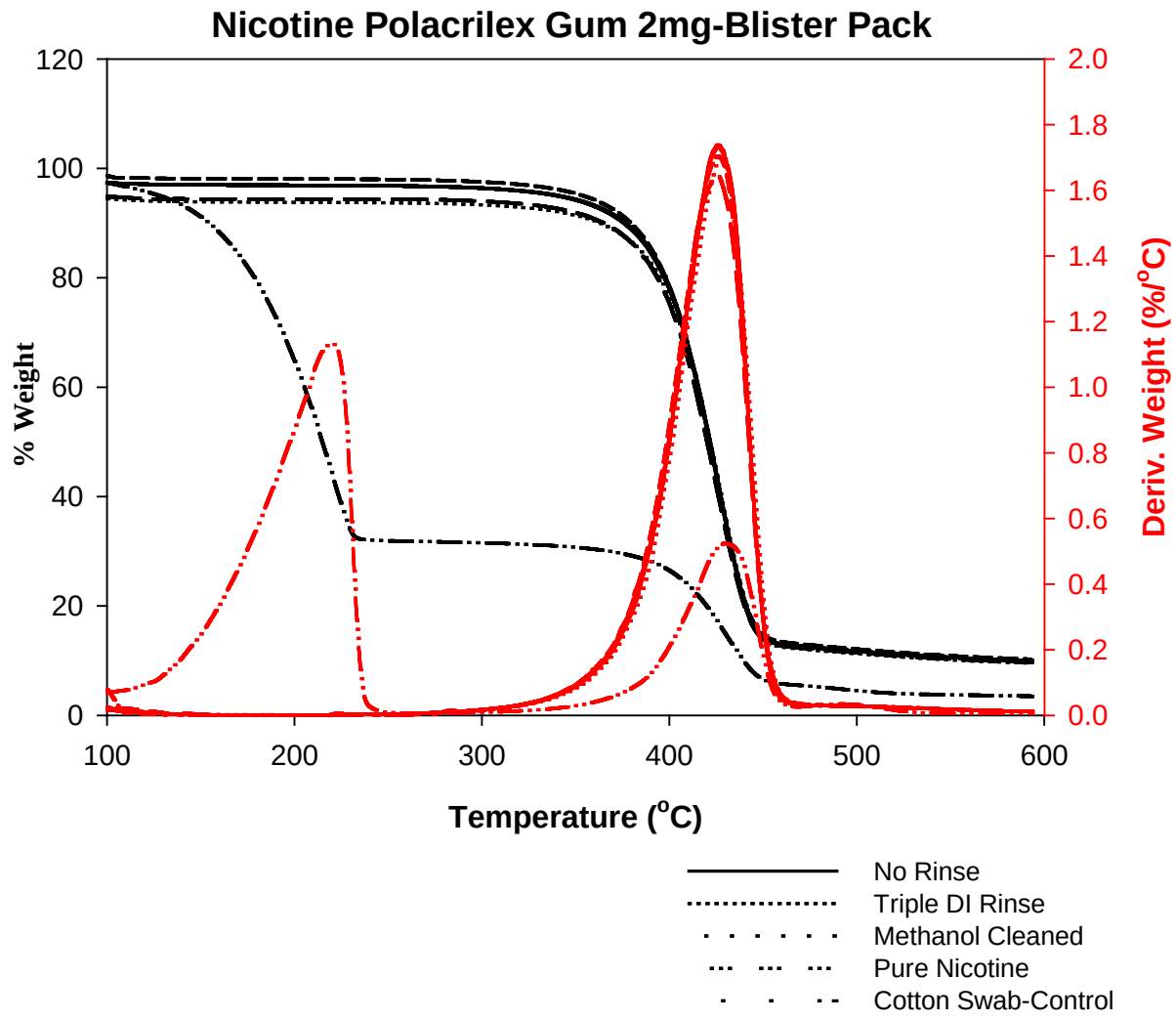


Figure B-9: Nicotine Polacrilex gum 2 mg, blister packs

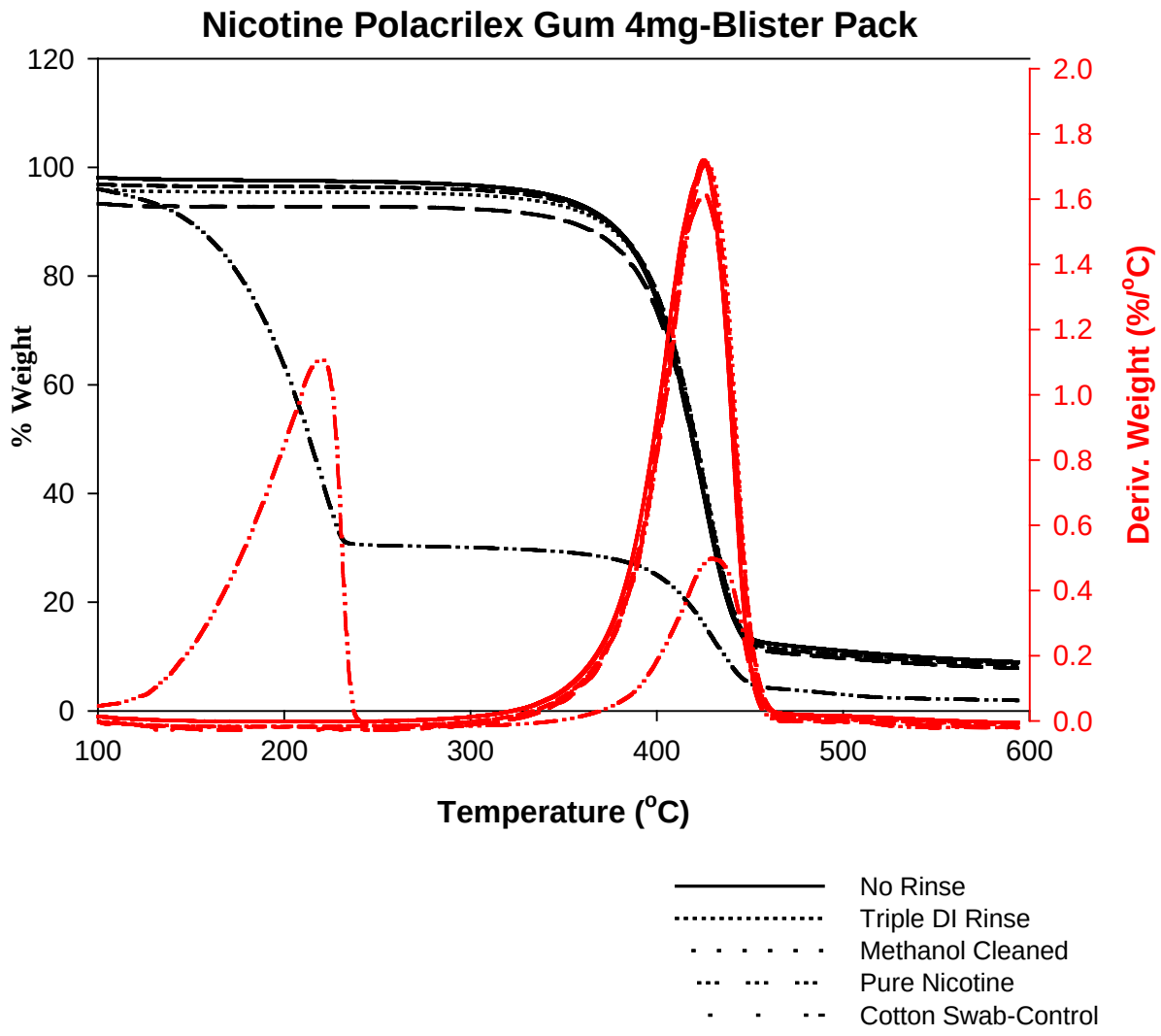


Figure B-10: Nicotine Polacrilex gum 4 mg, blister packs

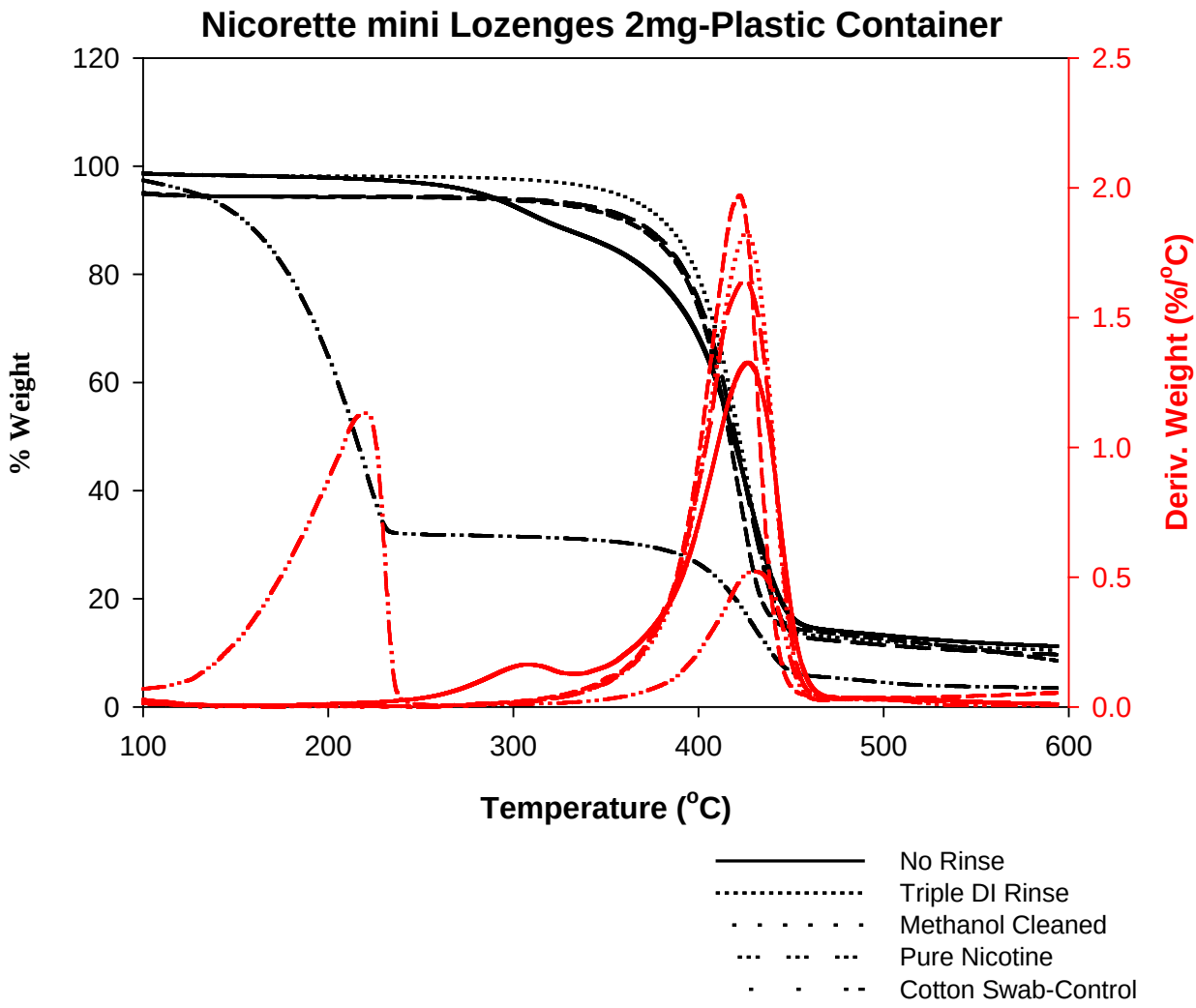


Figure B-11: Nicorette mini lozenges 2mg, plastic

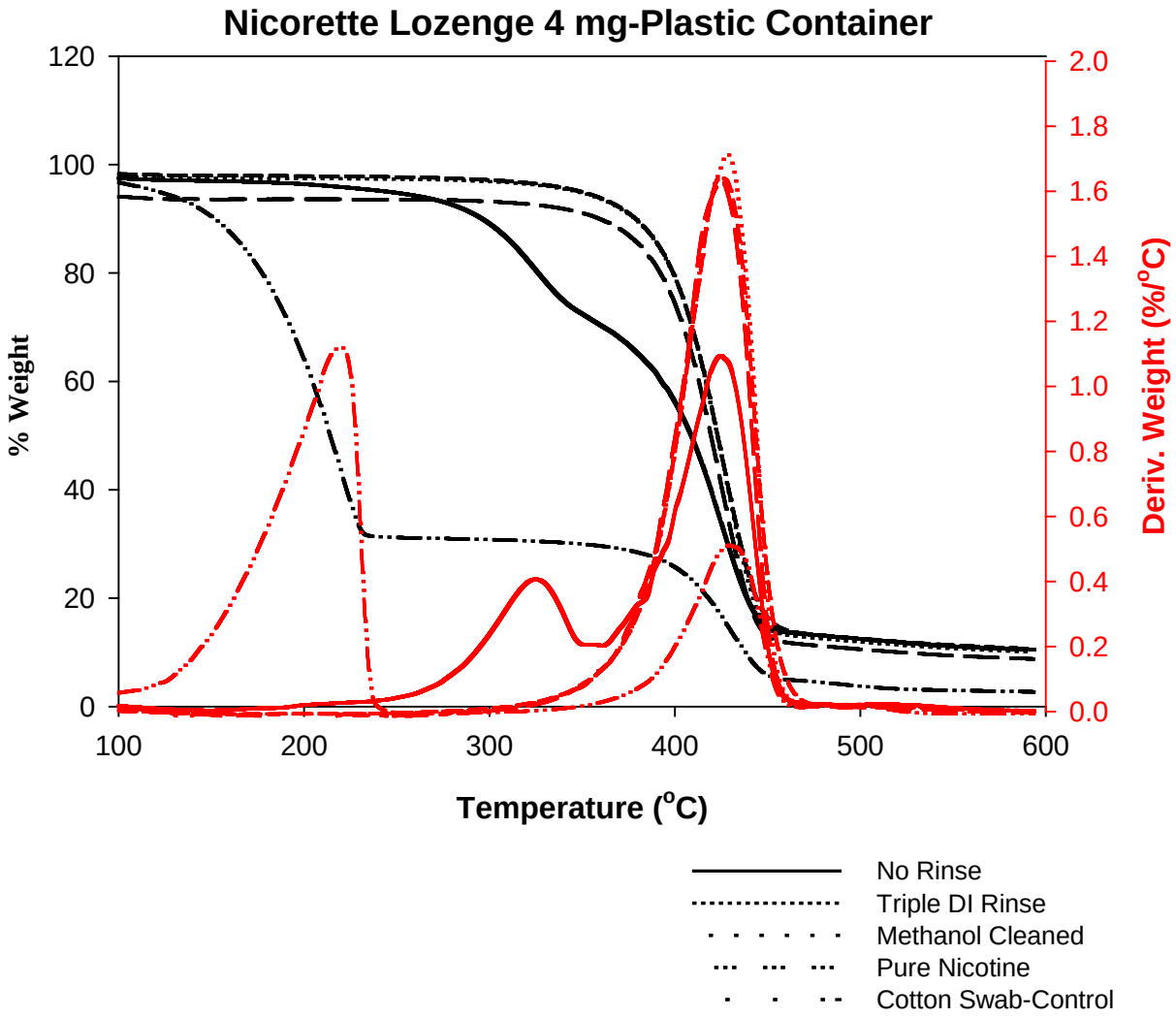


Figure B-12: Nicorette mini lozenges 4mg, plastic container

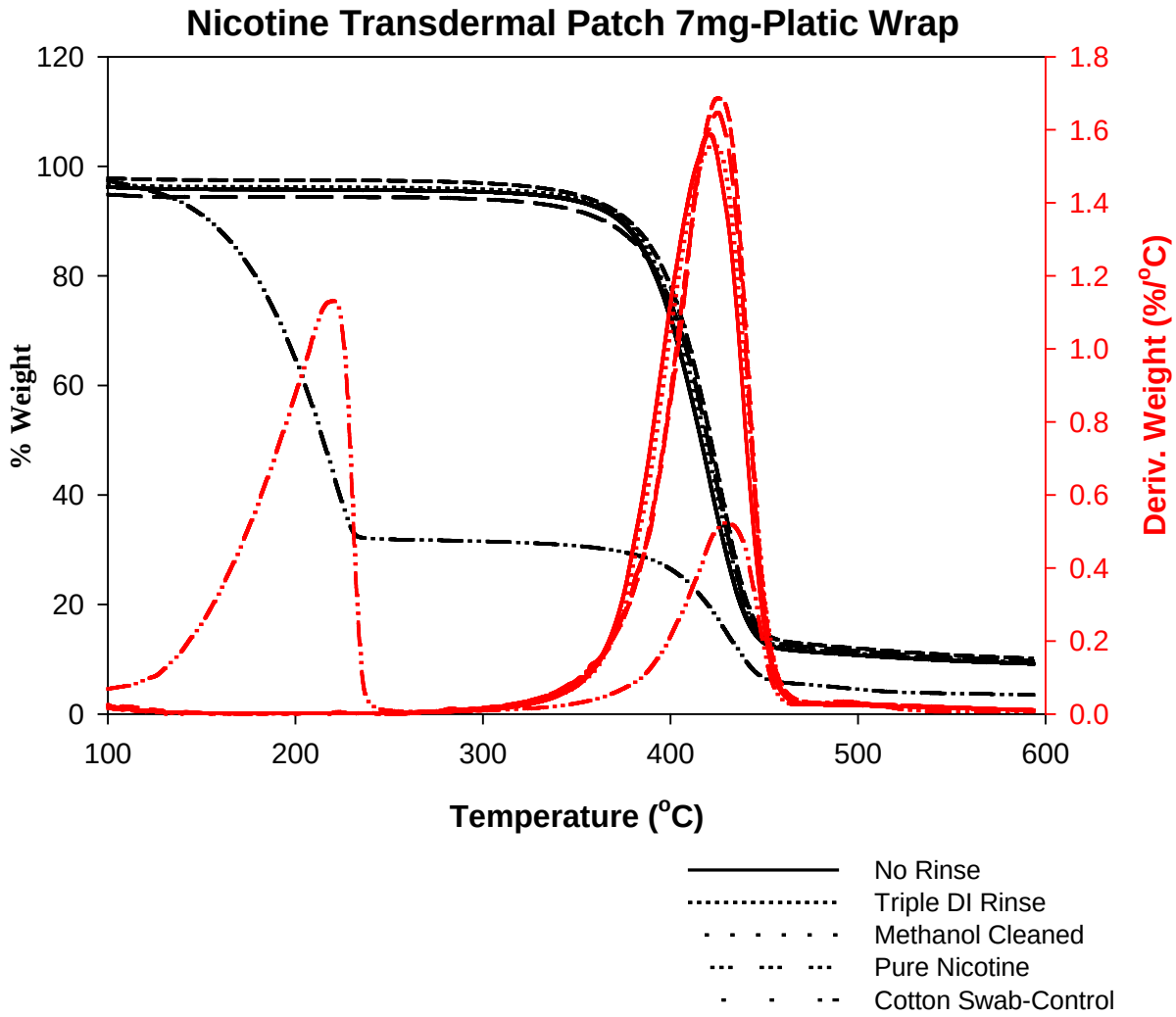


Figure B-13: Nicotine Transdermal Patch 7mg, plastic wrap

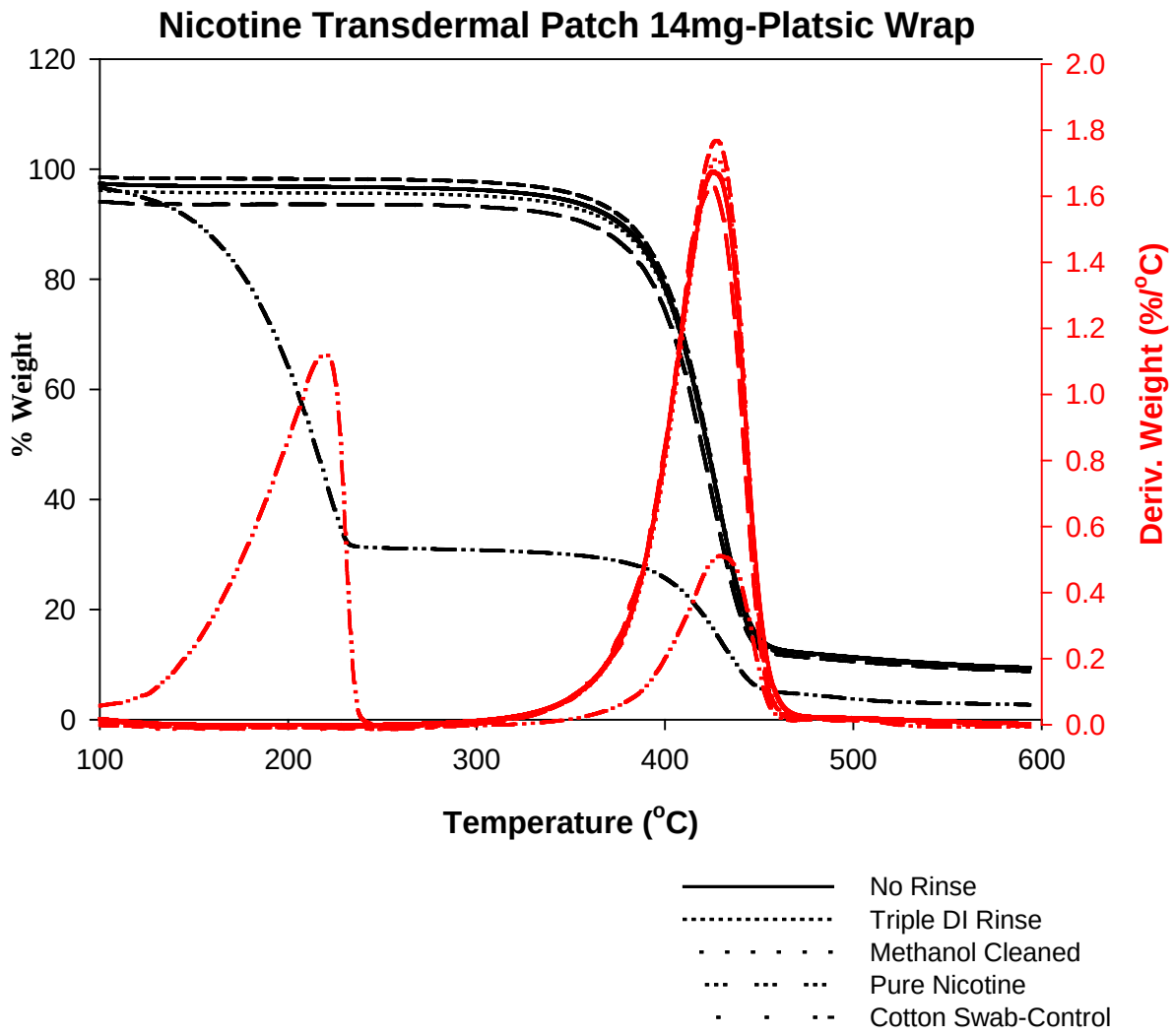


Figure B-14: Nicotine Transdermal Patch 14mg, plastic wrap

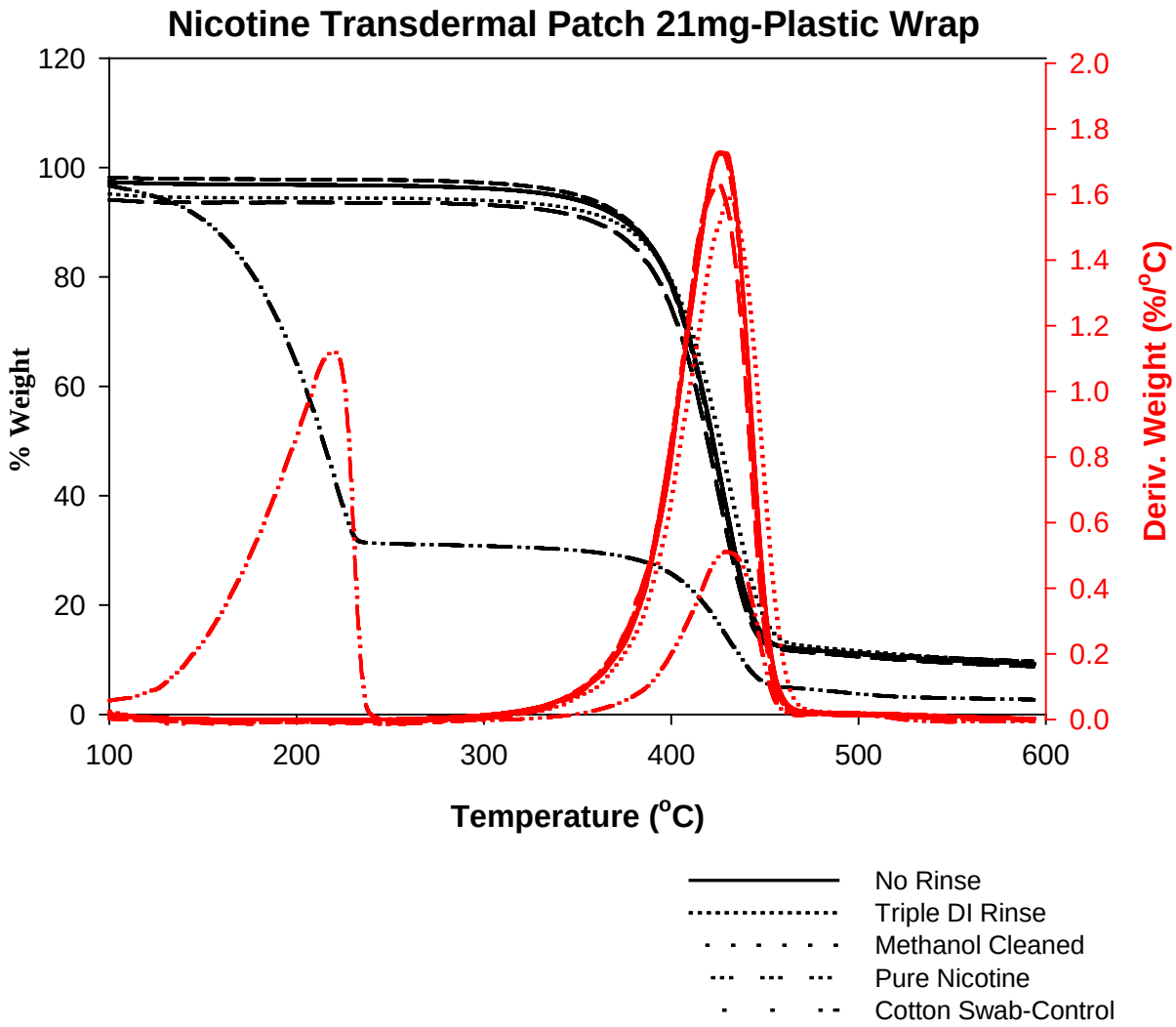


Figure B-15: Nicotine Transdermal Patch 21mg, plastic wrap

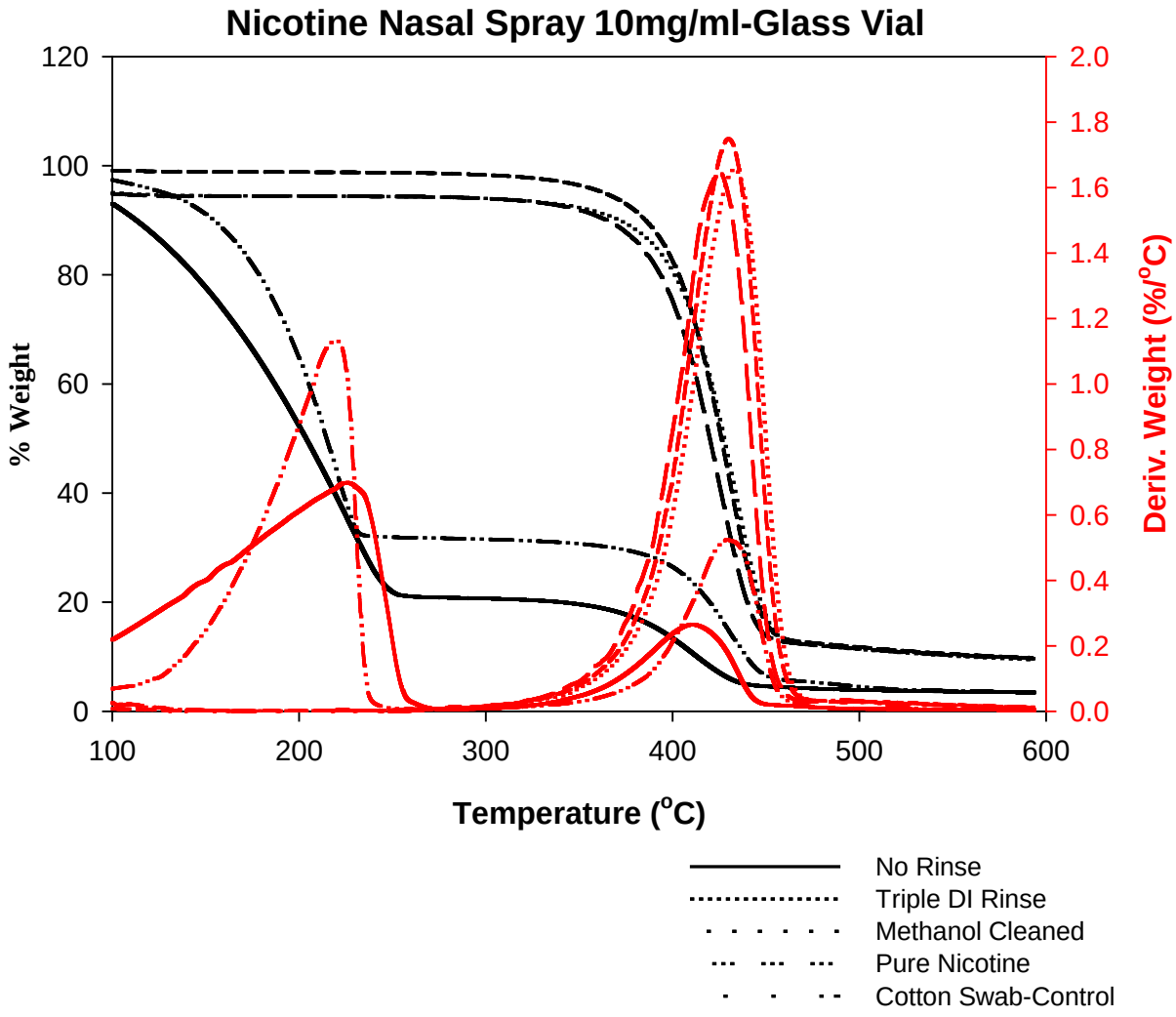


Figure B-16: Nicotine nasal spray 10 mg/ml, glass vial

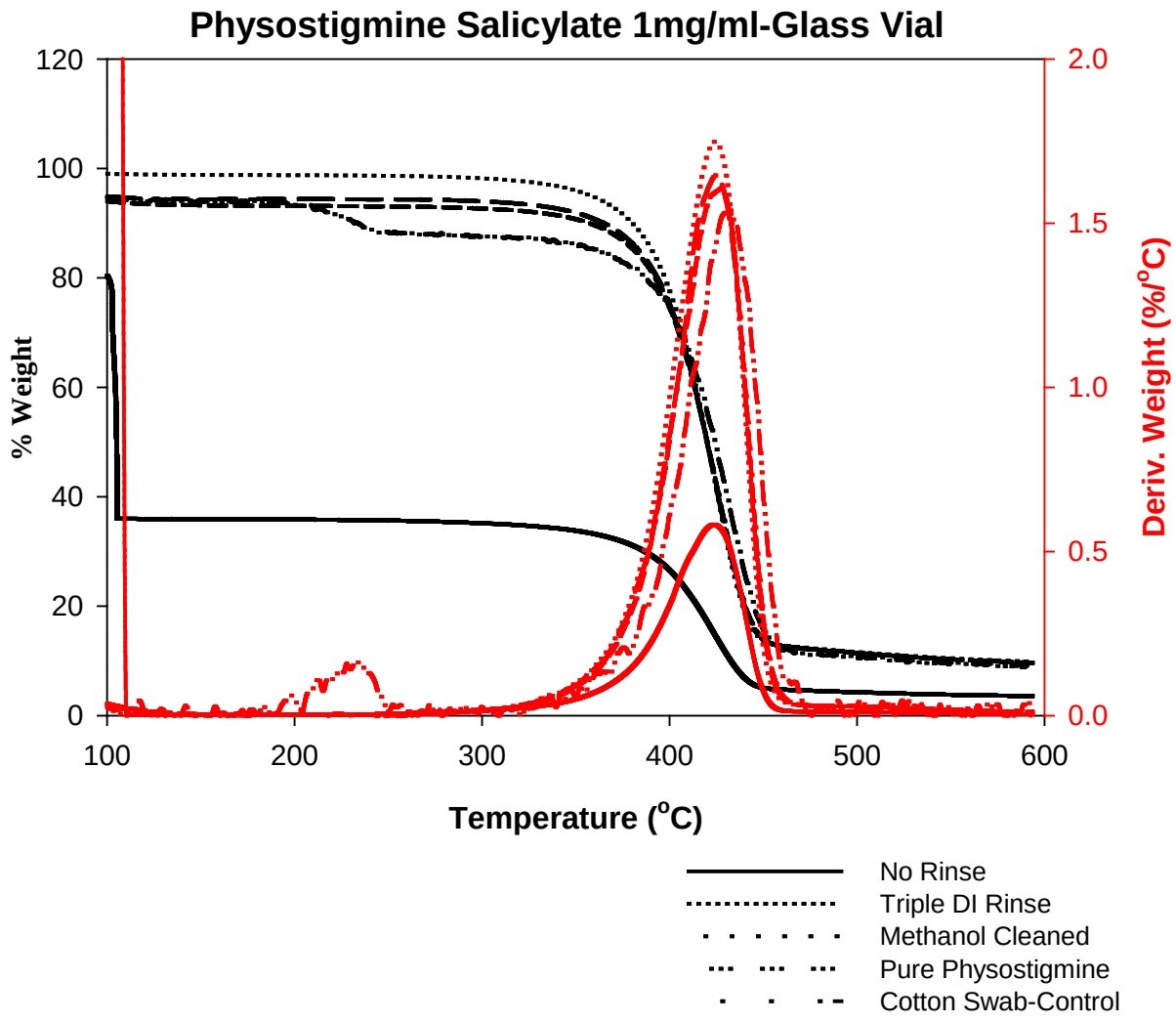


Figure B-17: Physostigmine Salicylate 1 mg/ml, glass vial

10 Appendix C

Appendix C

Table C-1: Summary of the $T_{max\ wt\ loss}$ for the pure compounds and the residuals in the medication containers

Active Compound	**Medication**	**$T_{max\ wt\ loss}$ (°C)****				**$T_{max\ Wt\ Loss}$ (°C)**	
		No Rinse		**Triple Rinse with Water**			
		Residuals	QC Check (Cotton piece)	Triple Rinse with Water	QC Check (Cotton piece)	Pure Compound	QC Check (Cotton piece)
Nicotine	Nicorette Gums 4 mg fruit chill	0±0	424±2	0±0	423±1	217±3	431±1
	Nicorette Gums 2 mg	0±0	425±0.6	0±0	424±1		
	Nicorette lozenges 4mg	324±0.7	426±2	0±0	427±0.9		
	Nicorette mini lozenges 2mg*	306	427	0	427		
	Nicotine gum polacrilex 2mg	0±0	425±0.8	0±0	427±0.3		
	Nicotine gum polacrilex 4mg	0±0	424±2	0±0	427±3		
	Nicotine nasal spray 10 mg/ml##	217±18	410±2	0±0	430±2		
	Nicotine transdermal patch 7 mg	0±0	426±0.4	0±0	422±0.2		
	Nicotine transdermal patch 14 mg	0±0	426±0.6	0±0	425±3		
	Nicotine transdermal patch 21 mg	0±0	428±3	0±0	428±3		
	Nicotine Inhaler $$	No experiments were conducted for this medication					
Warfarin Sodium	Jantoven 1 mg	0±0	423±2	0±0	423±1	313±3	430±1
	Jantoven 10 mg	0±0	422±2	0±0	424±0.4		
	Warfarin sodium 1 mg tablets	245±4	425±1	0±0	426±0.4		
	Warfarin sodium 5 mg tablets	239±2	423±0.7	0±0	425±0.9		
	Warfarin sodium 10 mg tablets	231±2	425±1	0±0	425±2		
	Warfarin sodium 2 mg blister packs	0±0	427±1	0±0	426±0.9		
Physostigmine salicylate	Physostigmine Salicylate	103±0.4	424±0	0±0	425±2	236±3	431±1

* Duplicate samples only were analyzed. The $T_{max\ wt\ loss}$ (°C) for the residuals were 307 and 305 for non-rinse samples and were 0 and 0 for the triple rinse with DI samples.

** The temperature at which the peak in weight loss occurs

Results are inconclusive. This residuals were in liquid form. All samples (non-rinsed, triple rinsed with DI and cleaned with methanol) were analyzed same day August 20, 2013 and there was no issue with the rinsed samples with regards to the cotton piece QC check. Therefore, it is not a calibration issue because the triple rinsed samples cotton peaks were in agreement with the specified range. The discrepancy observed here may be a result of some chemicals in the residual liquid that reacted with the cotton piece and changed its characteristics. Therefore, the results of this medication should be used with caution.
$$ The amount of residuals/cartridge =6 mg. This value is not experimentally determined. The manufacturer already mentioned on the package that every cartridge contain 10 mg and 4 mg delivered

Note:
$T_{max\ wt\ loss}$ temperature values were obtained from the TGA plot of each replicate and given values are the average of n=3 measurements, with uncertainty expressed as the standard deviation of n=3 measurements for each medication (except for Nicorette mini lozenges 2mg*).

Table C-2: Specifications of the pure active pharmaceutical compounds

Warfarin Sodium	**Nicotine**	**Physostigmine Salicylate**
Formula: $C_{19}H_{15}NaO_4$	**Formula:** L-Nicotine	**Formula:** $C_{15}H_{21}N_3O_2.C_7H_6$
CAS#: 129-06-6	**CAS#:** 54-11-5	**CAS#:** 57-64-7
Lot#: TKUB-RD	**Lot#:** A0315876	**Lot#:** GG01-FF0L
Molecular Weight: 330.31	**Code:** 181420050	**Molecular Weight:** 413.47
Purity:>98%	**Purity:** 99+ %	**Purity:** >98%
Company: TCI	**Company:** Acros Organics	**Company:** TCI

11 Appendix D

Appendix D

Quality Assurance Project Plan

for

Evaluation of P-Listed Pharmaceutical Residues in Empty Pharmaceutical Containers

Prepared by:
Pegasus Technical Services
Cincinnati, OH

Prepared under:
EPA Contract No. EP-C-11-006

QUALITY ASSURANCE PROJECT PLAN
CATEGORY II MEASUREMENT PROJECT

Evaluation of Methods for Disposal of P-Listed Pharmaceutical Containers to be Considered RCRA Empty

QUALITY ASSURANCE PROJECT PLAN APPROVAL LIST

U.S. Environmental Protection Agency Contract No. EP-C-11-006
Work Assignment 3-17

Prepared for:

Thabet Tolaymat, Ph.D.
Work Assignment Manager

U.S. Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory
Land Remediation and Pollution Control Division

Prepared by:

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Pegasus Technical Services Inc.
Cincinnati, OH 45219

Revision 1
December 4, 2013

Pegasus Technical Services, Inc. Concurrences:

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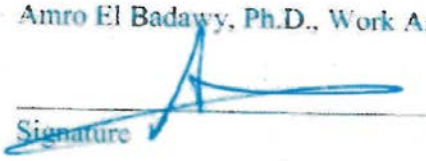

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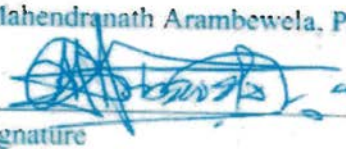
04/07/2014
Date

2. Mahendranath Arambewela, Ph.D., Pegasus On-Site Staff



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04/07/2014
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2. Steven Jones, ASQ CQA/CQE, Contract Quality Assurance Manager

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04/07/2014
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3. Raghuraman Venkatapathy, Ph.D., On-Site Technical Manager

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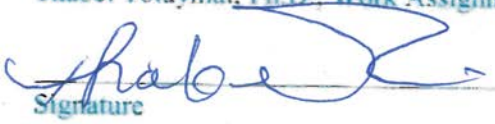
04/08/2014
Date

U.S. Environmental Protection Agency Approval for Implementation:

1. Thabet Tolaymat, Ph.D., Work Assignment Manager



Signature

4/10/14
Date

2. Jim Voit, LRPCD Quality Assurance Manager

_____ _____
Signature Date

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LIST OF ACRONYMS

AWBERC	Andrew W. Breidenbach Environmental Research Center
NRMRL	National Risk Management Research Laboratory
ORD	Office of Research and Development
SOP	Standard Operating Procedure
QA	Quality Assurance
QC	Quality Control
QAPP	Quality Assurance Project Plan
RCRA	Resource Conservation and Recovery Act
CFR	Code of Federal Regulations
OSWER	Office of Solid Waste and Emergency Response
TGA	Thermal Gravimetric Analysis
PI	Principal Investigator
RSD	Relative Standard Deviation
RPD	Relative Percent Difference
WA	Work Assignment

• PROJECT DESCRIPTION AND OBJECTIVES

o Project Description

Under the Resource Conservation and Recovery Act (RCRA), some pharmaceuticals are considered acute hazardous wastes since their sole active pharmaceutical ingredients are P-listed commercial chemical products (40 Code of Federal Regulations [CFR] Part 261.33). Hospitals and other healthcare facilities have struggled with RCRA requirements for empty containers when it comes to disposal of visually empty warfarin and nicotine containers. For example, nicotine and its salts that are used in nicotine gums, patches and lozenges are considered hazardous wastes and listed as P075; warfarin (when present at concentrations greater than 0.3%) and its salts that are used in Coumadin are also considered hazardous waste and listed as P001. When unused nicotine-based smoking cessation products (e.g., patches, gums and lozenges) and Coumadin are discarded, they must be managed as acute hazardous wastes in accordance with all applicable RCRA regulations. Furthermore, due to additional management requirements for P-listed wastes, any acute hazardous waste residues remaining in containers must be managed as hazardous unless the container has been rendered "RCRA empty" either by triple rinsing with water or by another method proven to achieve equivalent removal. Rendering empty pill bottles and other pharmaceutical containers (e.g., blister packs, ampoules, protective peel strips and packaging from medicinal patches, etc.) as "RCRA empty" is better than managing them as hazardous waste which is difficult and costly for the healthcare facilities, and it may not be necessary if the amount of residues is sufficiently small. However, in order to make any changes to the current P-listed empty container requirements for pharmaceuticals, more information is needed on residual wastes remaining in the empty containers after removal of the drug to determine if triple rinsing of the container is needed.

o Project Objectives

The purpose of this study is to ascertain if simply removing the drug (specifically nicotine, Coumadin and physostigmine) from its container is equivalent to triple rinsing the container. The U.S. Environmental Protection Agency (EPA) Office of Solid Waste and Emergency Response (OSWER) plans to address the issue of rendering these pharmaceutical packages RCRA empty through a rulemaking. Therefore, the objective of this study is to evaluate if the residues in fully dispensed (but not triple rinsed) containers and packaging contain the pharmaceutical active ingredient. In other words, to determine if simply removing the drug from its container (without rinsing) is equivalent to triple rinsing the container with water or other appropriate solvents. This objective will be achieved through the following steps:

- Measure the amount of residuals in pharmaceutical containers containing warfarin, physostigmine and nicotine medications after removing the drugs (no rinsing) and after triple rinsing the empty container.

- Use thermal gravimetric analysis (TGA) technique to verify the presence of active pharmaceutical ingredient in the residuals in a weight above the detection limit of the TGA balance (0.1 ug).

• ORGANIZATION AND RESPONSIBILITIES

o Responsibilities of Project Participants

Mr. Michael Moeykens serves as the EPA Project Officer for EPA Contract No. EP-C-11-006. Dr. Thabet Tolaymat is the EPA Principal Investigator (PI) responsible for technical direction, project goals, and the quality of the data generated. Ms. Kristin Fitzgerald of the Office of Solid Waste Emergency Response (OSWER) is the data end user. Mr. Jim Voit is the EPA Land Remediation and Pollution Control Division (LRPCD) Quality Assurance (QA) Manager responsible for review and approval of the quality assurance project plan (QAPP).
Dr. Karen Koran is the Pegasus Technical Services, Inc. (Pegasus) Project Manager. Dr. Raghuraman Venkatapathy is the Pegasus On-Site Technical Manager responsible for supervision of the Pegasus Team staff. Mr. Steven Jones, ASQ CQA/CQE, with Shaw Environmental & Infrastructure, Inc., is the Pegasus Contract QA Manager responsible for oversight of Pegasus Quality Program implementation, QA review of quality documents and deliverables, and project assessments. Dr. Amro El Badawy, Pegasus On-Site WA Leader, with the help of Dr. Mahendranath Arambewela, Pegasus On-Site Project Staff are responsible for day-to-day management and planning of research activities, sample collection, laboratory experiments, data analysis, and report preparation.

2.2. Project Organization and Distribution List

The project participants, contact information, and QAPP distribution list is provided in Table 2.1. A project organization chart is provided in Figure 2.1.

Table 2.1 Project Contacts and Distribution List

Name	Phone/email	Role
Mr. Michael Moeykens	(513) 569-7196 Moeykens.Michael@epa.gov	EPA Project Officer
Dr. Thabet Tolaymat	(513) 487-2860 Tolaymat.Thabet@epa.gov	EPA Principal Investigator
Ms. Kristin Fitzgerald	(703) 308-0522 Fitzgerald.Kristin@epa.gov	EPA OSWER End Data User
Mr. Jim Voit	(513) 487-2867 Voit.Jim@epa.gov	EPA LRPCD QA Manager
Dr. Karen Koran	(513) 569-7304 Koran.Karen@epa.gov	Pegasus Project Manager
Dr. Raghuraman Venkatapathy	(513) 569-7077 Venkatapathy.Raghuraman@epa.gov	Pegasus On-Site Technical Manager
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Dr. Amro El Badawy	(513) 569-7688 El-Badawy.Amro@epamail.gov	Pegasus On-Site WA Leader
Dr. Mahendranath Arambewela	513) 569-7688 Arambewela.Mahendranath@epa.gov	Pegasus On-Site Project staff

1.1. Project Schedule

The project schedule and milestones for main project activities are shown in Figure 2.2.

Table 2.2 Project Schedule

	Aug 2012	Oct 2012	Dec 2012	Feb 2013	Apr 2013	Jun 2013	Aug 2013	Oct 2013	Dec 2013	Feb 2014	Apr 2014
QAPP Preparation											
Sampling/ Data Collection											
Data Verification/Validation											
Monthly Reports											
Report Writing											
Report Submission											

2. SCIENTIFIC APPROACH

2.3. Sample Collection

An application will be filed with the Ohio Board of Pharmacy in order to obtain a license for purchasing the selected medications from a wholesaler. The board will issue a terminal distributor of dangerous drugs license to purchase and utilize dangerous drugs for scientific purposes within 30 days after receipt of the application. The license will be effective for twelve months from the first day of January of each year. The license will be renewed annually, if needed. Once the license is obtained, the various P-listed pharmaceutical containers/packaging (bottles, pouches, blister packs, etc.) containing unexpired nicotine, Coumadin and physostigmine will be purchased from a wholesaler. A variety of drug doses and types (pills, patches, gums, lozenges, etc.) as well as a variety of container types will be investigated.

The following records are required by the Ohio Board of Pharmacy for any laboratory that is given a license to utilize dangerous drugs for scientific purposes:

1. The name of each drug;
2. The form of the medication (e.g., powder, granulation, tablet, or solution);
3. The total number of form types received for each medication (e.g., number of tablets or volume of liquid) including the date and quantity of each receipt or manufacture, and the name, address, and registration number, if any, of the person from whom received;
4. The total quantity of each medication;
5. The quantity utilized in any manner by the laboratory including the date and manner of utilization, and the name, address, and registration number, if any, of each person to whom provided for utilization.

The above mentioned records will be recorded in the project logbook CH 276 which will be signed by the WA Leader and witnessed by the EPA PI. The issued Ohio Board of Pharmacy License number is LR. 022271550. The purchased pharmaceuticals under this license will be stored in laboratory 131A located at the Center Hill Research Facility. The access to Lab 131A is limited as there is an access code that is given to a few number of known individuals.

2.4. Methodology

As previously stated, this study aimed mainly at evaluating the necessity of triple rinsing pharmaceutical containers (specifically nicotine, coumadin and physostigmine containers) after removing the drugs in order for the container to be considered “RCRA empty”. If triple rinsing is not required, then simply emptying the drugs from a container makes it RCRA empty. This section presents the experimental approach to conduct this evaluation.

In the current study, three drugs will be evaluated, 1) warfarin sodium, 2) nicotine, and 3) physostigmine salicylate. Various drug packaging /drug concentrations of each drug type will be purchased from TirHealth outpatient pharmacy located in Cincinnati, OH. Examples of drug packaging types include blister packs, plastic bottles, glass vials and glass ampoules. A total of 19 different types of drug packaging/drug concentration will be investigated in this study (7 for warfarin sodium, 11 for nicotine and 1 for physostigmine salicylate

3.2.1 Experimental Approach

- The medication (tablets, pills, lozenges, etc…) will be removed from the container in a way to simulate use. The removed medication will be discarded and treated as hazardous waste.
- The empty containers will be exposed to one of three conditions:
  - No rinse
  - Triple rinse with deionized water (DI)
  - Cleaned container (negative controls). Preparation of the negative controls is further discussed in Section 3.2.2.

  Triplicate containers will be evaluated under each one of the above 3 conditions.
- The amount of residuals in each rinsed container will be determined as follows:
  - Using a sensitive balance (Mettler Toledo AB104-S, readability of 0.1 mg), determine the weight of the empty container (1) before and (2) after treatment. The difference in weight (1 and 2) represents the amount of residuals.
- To check if the residuals in the empty container contain the active pharmaceutical ingredient:
  - The residuals in the empty container will be collected using a cotton tip applicator (Figure 3.1). The cotton tip will be used to swab the empty container's walls to collect any residuals.

Figure 3.1 Picture of the cotton tip applicator

  - The cotton piece (~ 10 mg) will be detached, with gloved-hand , from the wooden stick and loaded into the TGA sample pan (Figure 3.2) (pan capacity is 1gm). Figure 3.3 presents a schematic for the steps performed to collect the residuals from the containers on the cotton tip and loading it to the Thermal Gravimetric Analysis (TGA) (TA Instruments, 2950 TGA) sample pan.

Figure 3.2 Picture of the TGA sample pan

Figure 3.3 Schematic of sample preparation for TGA analysis

The TGA (Figure 3.4) measures the weight loss of the cotton piece loaded with residual (if any) as a function of temperature. The TGA will be programmed to heat the sample at a rate of 20ºC/min to 600ºC. The TGA balance readability is 0.1 ug.

""

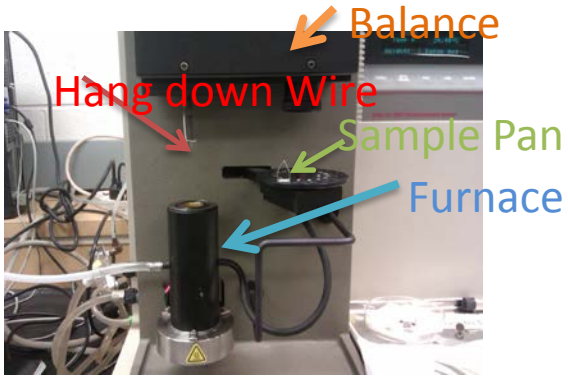

Figure 3.4 TGA components

The TGA is a technique in which the loss of mass of a substance is monitored as a function of temperature or time as the sample specimen is subjected to a controlled temperature program in a controlled atmosphere. The TGA instrument consists of a sample pan that is supported by a precision balance and a furnace. The sample pan containing the sample is heated to a specified temperature. The loss of the sample weight is monitored as a function of temperature. TGA relies on a high degree of precision in three measurements: weight, temperature, and temperature change. As a result of heating the sample to high enough temperature, some residuals decompose into gas, which dissociates into the air. The TGA analysis will generate a plot of % weight loss (Y-axis) and temperature (X-axis). The temperature at which the peak in weight loss occurs for the collected residual from the empty drug container will be compared to that of the pure active pharmaceutical compound. If the temperature at which the peak weight loss of both the residual and the pure compounds is similar, then the residuals contain the active ingredient and if not then the residuals is composed of something else. It should be noted that the TGA data is qualitative which means the TGA results will not be used to quantify the amount of active pharmaceutical ingredient in the residuals; it will rather be used to verify the presence of absence of the active ingredient in the residuals.

- The following controls will be analyzed on the TGA along with the samples:
    - Clean cotton piece without residuals
    - Negative control: clean empty containers and clean cotton piece
    - Positive control: pure active compounds of warfarin sodium, nicotine or physostigmine salicylate loaded on a cotton piece.

3.2.2 Example of TGA Results

The TGA analysis of the clean cotton piece is presented in Figure 3.5. The 1st derivative of the weight loss as a function of temperature (red line in Figure 3.5) shows the temperature at which the peak in weight loss occur as a result of heating the cotton piece in the TGA furnace to 600 ^{o}C. Based on Figure 3.5, the maximum weight loss of the cotton piece occurred at 425^{o}C. When loading pure nicotine on the cotton piece, an additional peak of weight loss occurred at 215 ^{o}C as presented in Figure 3.6. Thus, if the residuals in the empty nicotine-based drug container showed a peak in weight loss at 215 ^{o}C, then the residuals contain the active ingredient and if not, the residuals may still have nicotine but below the detection of the TGA balance which is 0.1 ug. Figure 3.7 presents the TGA results of the residuals collected from nicotine lozenges after loading the residual on a clean cotton piece. The results showed that the residuals have a peak in weight loss at 305 ^{o}C which is different than

that of the pure nicotine (215 ºC). This means that the residuals may have nicotine below the TGA balance detection but the majority of the residuals are something else.

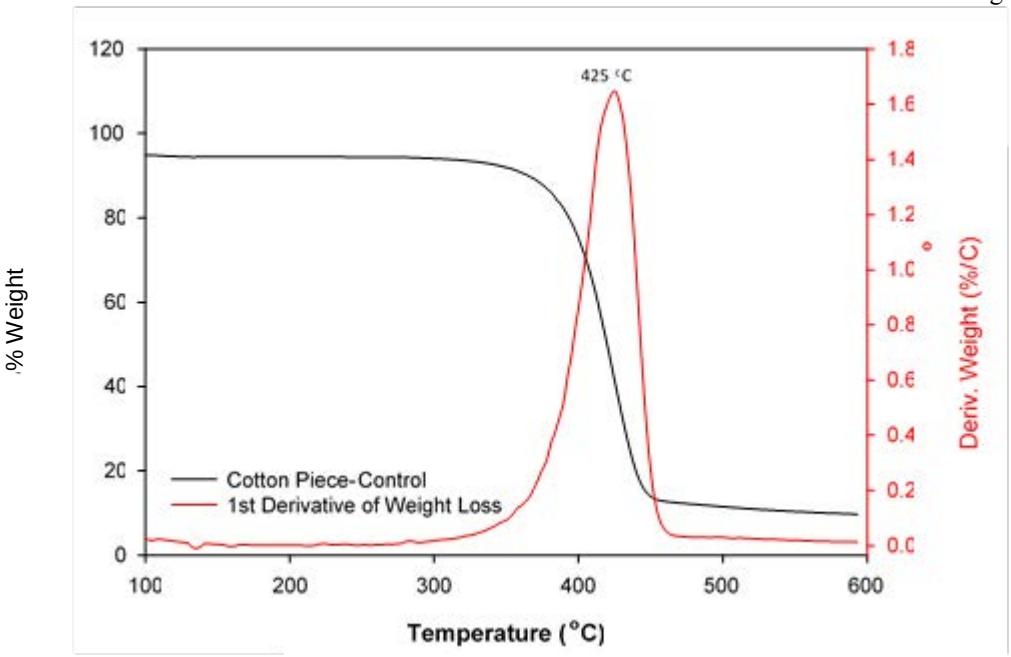

Figure 3.5 TGA analysis of clean cotton piece

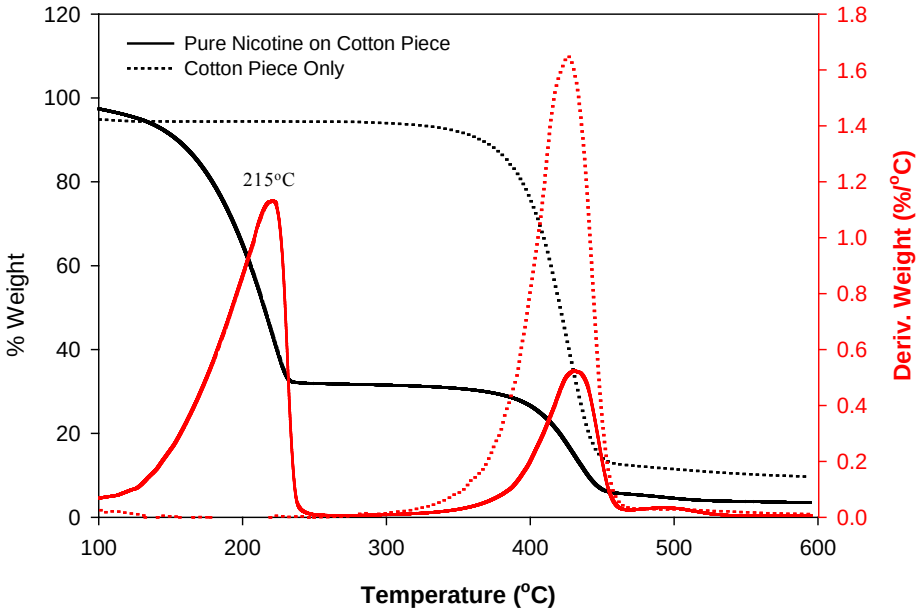

Figure 3.6 TGA analysis of pure nicotine loaded on cotton piece

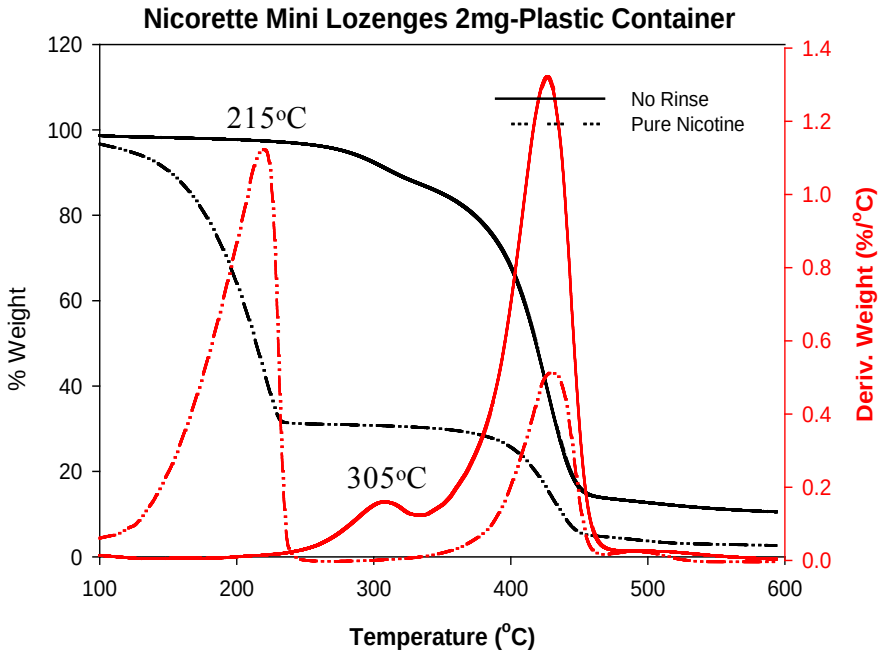

Figure 3.7 TGA analysis of residuals of nicotine lozenges as compared to pure nicotine

3.2.3 Temperature of Maximum Weight Loss of Pure Pharmaceutical Compounds

The temperature at which the maximum weight loss occurs will be used to verify the presence of the active pharmaceutical compounds in the residuals. This will be achieved through comparing the temperature at which the maximum weight loss occurs for the pure pharmaceutical compounds (presented in Table 3.1) to that of the residuals.

Table 3.1 Temperature for Maximum Weight Loss*

Pure Compound	CAS #	Temperature for maximum weight loss on TGA (°C)*	Acceptance Criteria (°C)[6]
Warfarin Sodium	129-06-6	313	±5
Physostigmine Salicylate	57-64-7	236	±5
Nicotine	54-11-5	217	±5
Clean Cotton Piece	NA	427	±5

***** These values are determined using the TGA in our laboratory utilizing the same method of analysis used to analyze the residual samples

3.2.4 Preparation of the Clean Containers (Negative Control)

1. Empty the container containing the drug.
2. Rinse the container 3 times with methanol
3. Dry the container in a dessicator and weigh out the dry container.

4. Repeat steps 2-3 until the weight of the dry container becomes constant.
5. Store the clean container in double Ziploc bags until further use.
6. In order to verify that the chosen solvent does not affect the bottle material, the following preliminary experiments will be conducted:
    1. Repeat steps 2-4 with at least one other type of solvent (e.g. acetone).
    2. It will be confirmed that the methanol rinse does not affect the bottle material if the dry weight measured in step 4 using the other rinsing solutions is similar to the dry weight obtained from the methanol rinse.

3. SAMPLING PROCEDURES

4.1. Sampling Strategy

Table 4.1 Sampling Schedule

Parameter	Type of Measurement	Type of medication	Total Number of packages	Number of samples per package	Number of positive control
Weight of residuals	Non-Critical	3	19	12*	NA[#]
Presence of active pharmaceutical ingredient in residuals	Critical	3	19	12*	9**

*****3 not rinsed containers, 3 triple rinsed with water, 3 cleaned with methanol and 3 cleaned with other organic solvent. The cleaned containers will serve as negative controls. NA: not applicable. **triplicate of each drug type (warfarin sodium, nicotine and physostigmine)

As previously presented in Section 3.2.1., a total number of 19 drug packages will be investigated in the current study. For each one of the 19 packages, 12 containers will be tested: 1) triplicate containers with no rinse, 2) triplicate containers will be rinsed with water, 3) triplicate containers will be cleaned from residuals using methanol and one other organic solvent (e.g. acetone) and will serve as negative controls. For each drug type (i.e. warfarin sodium, nicotine, and physostigmine salicylate) triplicate samples of the pure active pharmaceutical ingredient will be analyzed on TGA and will be used as positive control.

4.2. Sample Handling and Storage

Table 4.2 Sample Container, Preservation and Holding Times

Parameter	Quantity of Sample	Sample Collection	Preservation	Max. Holding Time
Weight of residuals	Variable	NA[*]	No Preservation	Analyze Directly
Presence of active pharmaceutical ingredient in residuals	Variable	Swab residuals on Cotton Tip	No Preservation	Analyze Directly

***** NA: Not Applicable. The empty container will be weighted out before and after rinsing. The difference in weight will be the amount of residual.

4.3. Sample Labeling

The container under investigation will be labeled to include the following information: container type, drug type, drug concentration, container condition (e.g., rinsed, non-rinsed, negative control), date and time of sampling, the test that will be performed on this sample and the initials of the personnel who processed the sample.

3. MESUREMENT PROCEDURES

The analyses methods are summarized in Table 5.1. Standard Operating Procedures (SOP) referenced in the Table are provided in Appendix A of this QAPP.

Table 5.1 Outline of Analysis Methods

Parameter	Measurement	Instrument	Analytical Method/SOP
Weight of residuals	Non-Critical[#]	AB104-S Balance (Mettler Toledo)	SOP #1
Presence of active pharmaceutical ingredient in residuals	Critical	Hi Res TGA 2950, TA Instruments	SOP #2

The data for the wieght of residuals generated under this QAPP should not be used for rule-making as the purpose of this measurement is only to provide an approximate range of residuals present in the containers. Sample package weights may differ greatly, which means that the detection limits on a weight/weight basis (w/w) will vary significantly and the precision of the balance used in the study will be impacted. Thus, the balance may not be sufficient to generate accurate residual data

4. QUALITY METRICS (QA/QC CHECKS)

Instruments/equipment will be maintained in accordance with the EPA ORD Policies and Procedures Manual, Section 13.4, *Minimum Quality Assurance (QA)/Quality Control (QC) Practices* for ORD Laboratories Conducting Research, and in accordance with the Standard Operating Procedures (SOPs) and analytical methods shown in Table 5.1. All analytical data will be collected in accordance with the QA/QC procedures specified in this QAPP. Table 6.1 summarizes the QA/QC checks, acceptance criteria, and corrective actions for each analysis. The data quality indicators for the analyses are defined below.

Accuracy (bias): is broadly defined as how close the analyses will come to the true concentration in the sample. The accuracy of measurements, incorporating a standard reference material or a second source standard, will be calculated as percent recovery as follows.

$$\%R = \frac{Cm}{Ca} \times 100$$

Where: C_m = measured value of the check standard.

C_a = certified value of the check standard.

***Precision*:** Precision is broadly defined as the scatter within any set of repeated measurements. Laboratory replicates will be used to ensure precision. For samples that are measured in triplicate or higher, the precision will be measured as the relative standard deviation (RSD).

The relative standard deviation between replicates will be calculated as follows:

$$\% RSD = (\frac{S}{y'}) \times 100$$

Where: S = Standard deviation

y' = Mean of the replicates

Representativeness: is the extent to which measurements actually depict the true condition or population being evaluated. The measurement of the residuals in the pharmaceutical containers will be conducted using the container as a whole and not on portions of it. This will ensure a high representativeness of the measurement. With regards to the TGA analysis on the residuals, a cotton piece will be used to swab all the internal walls of the containers in order to ensure the representativeness of the measurement for the actual residuals in the containers.

Completeness: is number of data points meeting all DQO / total number data points. A 90 % completeness is required for this project. The completeness (C) will be calculated as follows:

$$\%C = \frac{v}{T} \times 100$$

Where: v = the number of actual measurements

T= the number of planned measurements

Comparability: is the extent to which data from one study can be compared to past data from the current project or data from another study. Data comparability will be maintained through the use of defined and consistent sampling and analytical procedures. The SOPs defined in this QAPP will be systematically followed each time a sample is being processed.

Table 6.1 Summary of QA/QC Checks

Parameter	Measurement	QC Check	Method	Frequency	Acceptance Criteria	Corrective Action
Weight of residuals	Weight	Accuracy	Measure a standard weight	Once per day before conducting the measurements	± 0.1mg of the actual weight	1- Investigate problem 2- Use another calibrated balance 3- Sample analysis will not begin until all calibration checks are within the acceptance criteria
Presence of active pharmaceutical ingredient in residuals	Temperature	Temperature calibration	1 point calibration	Initially (once at start of the project data collection) and as needed**	± 5 of the curie temperature of the standard metal[6]	1- Investigate problem 2- Re-calibrate 3- Sample analysis will not begin until all calibration checks are within the acceptance criteria
	Weight	Calibration Check	2 point calibration	Initially (once at start of the project data collection) and as needed	± 0.1 mg of the actual weight	1- Investigate problem 2- Re-calibrate 3- Sample analysis will not begin until all calibration checks are within the acceptance criteria
		Accuracy	Measure a standard weight	Once per day before and after conducting the measurements	± 0.1 mg of the actual weight	1- Investigate problem 2- Re-calibrate 3- Sample analysis will not begin until all calibration checks are within the acceptance criteria

** As needed: temperature calibration is needed when the temperature of the peak weight loss of the cotton piece is not in the range of 427 ± 5 °C.

5. ASSESMENT AND OVERSIGHT

7.1 Assessments and Responses Actions

EPA will conduct Technical Systems Audits (TSAs) on laboratory activities which will focus on the critical target analytes. Detailed checklists, based on the procedures and requirements specified in this QAPP, related SOPs, and EPA Methods will be prepared and used during these TSAs. These audits will be conducted by the EPA/NRMRL QA Management Team or by QA support contractors with oversight by the QA Management Team. Report of this activity will be generated and included in the project record, including response to any findings or observations. Data Quality Audits (DQAs) will be conducted on a minimum of 25% of the datasets generated for this project for the critical target analytes. These audits will be conducted by the EPA/NRMRL HF QA Management Team or by QA support contractors with oversight by the QA Management Team. See Section 8 for additional discussion on ADQs.

Assessors do not have stop work authority; however, they can advise the EPA PI if a stop work order is needed in situations where data quality may be significantly impacted, or for safety reasons. The PI makes the final determination as to whether or not to issue a stop work order. For TSA and DQA reports that identify deficiencies requiring corrective actions, the audited party must provide a written response to each Finding and Observation to the PI, which shall include a plan for corrective action and a schedule. If the audited party is a contractor, then the response shall be delivered to the EPA PI. The PI is responsible for ensuring that audit findings are resolved. The QA Management Team will review the written responses to determine their appropriateness. If the audited party is other than the PI, then the PI shall also review and concur with the corrective actions. The QA Management Team will track implementation and completion of corrective actions. After all corrective actions have been implemented and confirmed to be completed; the QA Management Team shall send documentation to the PI that the audit is closed. Audit reports and responses shall be maintained by the PI in the project file and the QA Management Team in the QA files.

6. DATA REVIEW, VERIFICATION, AND VALIDATION

6.1. Data Reporting

Table 8.1 summarizes the reporting units for the measured parameters. The analyst will reduce the results to the appropriate reporting units. The analysis results will be recorded in a laboratory notebook and each page will be dated and signed by the person who performs the analysis, then, those data will be fed manually to Excel spreadsheets for statistical analysis. Calculations (if any) will be checked initially for errors by the analyst and then sent to a second editor for review.

Table 8.1 Reporting Units

Parameter	Unit
Weight of residuals	ug
Presence of active pharmaceutical ingredient in residuals	NA*

*NA: Not Applicable. For this parameter, the temperature at which the weight loss peak of residuals occur will be compared to the temperature of the weight loss peak for pure active compound.

8.2. EPA Data Review, Verification, and Validation

Criteria that will be used to accept, reject, or qualify data will include specifications presented in this QAPP. Data will not be released outside of NRMRL until all study data have been reviewed, verified and validated as described in this QAPP. The PI is responsible for deciding when project data can be shared with interested stakeholders upon approval by the NRMRL Lab Director.

Data verification will evaluate data at the data set level for completeness, correctness, and conformance with the method. Data verification will be done by those generating the data. This will begin with the analysts in the laboratory, monitoring the results in real-time or near real-time. The WA leader shall contact the PI upon detection of any data quality issues which significantly affect sample data. They shall also report any issues identified in the data report, corrective actions, and their determination of impact on data quality.

Data reports are reviewed by the PI and the WA leader for completeness, correctness, and conformance with QAPP requirements. All sample results are verified by the PI to ensure they meet project requirements as defined in the QAPP and any data not meeting these requirements are appropriately qualified in the data summary prepared by the PI (or in the work assignment deliverables prepared by contractors that will be used by the PI). See Section 8.4 for the Data Qualifiers. The Contract Laboratory Program guidelines on organic (EPA, 2008) and inorganic (EPA, 2010) methods data review are used as guidance in application of data qualifiers.

Data validation is an analyte- and sample-specific process that evaluates the data against the project specifications as presented in the QAPP. Data validation (i.e., audit of data quality) will be performed by a party independent of the data collection activity. Data summaries for the critical analytes that have been prepared by the contractor as well as laboratory data reports and raw data shall be provided to the Pegasus on-site Technical Manager, who will coordinate the

data validation. NRMRL SOP #LSAS-QA-02-0, "Performing Audits of Data Quality" will be used as a guide for conducting the data validation. The outputs from this process will include the validated data and the data validation report (DAQ Report). The report will include a summary of any identified deficiencies, and a discussion on each individual deficiency and any effect on data quality and recommended corrective action.

8.3 Pegasus Data Review, Verification, and Validation

Data verification and validation is performed following the guidance provided in the EPA guidance document entitled, *Guidance on Environmental Data Verification and Validation*, EPA QA/G-8.

Initial data assessment is conducted by an analyst who is knowledgeable regarding the WA Quality requirements. The analyst determines that samples have been analyzed, calibration and QC data requirements have been met, and the data are ready for verification. This assessment is documented on the data summary sheet.

A complete verification (100% of the data) is conducted by knowledgeable personnel other than the analyst, as assigned by the Project Leader, QA Manager, or On-Site Technical Manager. This verification is documented on the cover of the data summary. Data verification includes review of the data for completeness, correctness, and technical compliance as summarized below.

- Completeness
    - The data package received contains the documentation listed in the data validation section (below).
    - Forms and other required information have been completed.
    - All expected samples and analyses were reported.
    - Relevant information for each analysis, including QC results and supporting documentation, are included in the data package.
- Correctness
    - Results have been transcribed correctly to the reporting sheets.
    - Sample results are supported by valid QC.
    - Missing results and QC outliers have been noted.
- Technical compliance
    - Sample hold times were met.
    - The correct analytical method was used for each analysis, as specified in the QAPP.
    - The samples were properly preserved in accordance with the requested method.
    - Calculations, QC frequencies, and acceptance criteria applied to the data are the same as those specified in this QAPP.

Ten percent of the spreadsheet cell calculations will be manually verified. Also, 10% of spreadsheet cell calculations will be reviewed using the Excel formula review functions to trace precedents and dependent cells. Data validation will be conducted by qualified individuals (or organizations) that are sufficiently independent of those who performed the work, but are collectively equivalent in technical expertise. Data validation is conducted to ensure that activities are technically adequate, competently performed, properly documented, and satisfy established technical and quality requirements. The Pegasus Contract QA Manager is responsible for ensuring that assigned data validators are sufficiently independent to perform the validation.

Data validation tasks begin with a review of the QAPP requirements. The data to be verified include standards data, initial calibration data, continuing calibration data, sample results, and QC data.

Additional validation may be recommended if significant anomalies are detected during the 10 percent review. Significant anomalies may include calibration inconsistent with method and/or WA requirements, replicate analysis outside RPD limits, or calculation errors.

8.4 Data Qualification

Data qualification is an integral component of data reporting, review and validation. During data reporting and review, qualifiers are applied to ensure the laboratory has provided data of known quality. During data validation, qualifiers are applied to alert the data end user to quality problems that may impact the usability of the data. Data qualifiers may be assigned to particular sample results based on available information, including: laboratory QC, unavoidable analytical interference, laboratory data summary information, etc. The data qualifiers and other data descriptors to be used in this project are below in Table 8.1 and 8.2.

Table 8.1 Data Descriptors

Descriptor	Definitions
NA	Not Applicable (See QAPP)
NR	Not Reported by Laboratory or Field Sampling Team
ND	Not Detected
NS	Not Sampled

Table 8.2 Data Qualifiers

Qualifier	Definitions
U	The analyte was analyzed for, but not detected above the reported sample quantitation limit.
J	The analyte was positively identified; the associated numerical value is the approximate concentration of the analyte in the sample.
J+	The result is an estimated quantity, but the result may be biased high.
J-	For both detected and non-detected results, the result is estimated but may be biased low.
B	The analyte is found in a blank sample above the quantitation limit, and the concentration in the sample is less than 10 times the concentration found in the blank.
H	The sample was prepared or analyzed beyond the specified holding time. Sample results may be biased low.
*	Relative percent difference of a field or lab duplicate is outside acceptance criteria.
R	The sample results are rejected due to serious deficiencies in the ability to analyze the sample and meet QC criteria. The presence or absence of the analyte cannot be confirmed.

8.5 Reconciliation With User Requirements

The data will be evaluated to check if they conform to the QA objectives of the project. A statistical assessment for accuracy, precision, and completeness will be performed. All analyses will be required to meet data quality objectives before formulation of the final report. Where failures are observed in the individual methods, data will be marked as suspect.

Sample data will be presented in tabular format or in figure. All parameters will be reported along with the mean, standard deviation and range, when applicable. Tabular data summaries will be included in the main discussion of the reports.

8.6 Data Summary, Analysis and Storage

The data to be managed in this project are the TGA instrument data files, spreadsheets for manually imported data for the weight of residuals, printed hard copy of the TGA data, the laboratory notebook and the data analysis files. The data analysis files will be prepared using Microsoft Excel and Sigmaplot Software. Microsoft Excel will be used to summarize the data and calculate mean and standard deviation of the weight of the residuals based on the triplicate samples analyzed for each condition. The TGA data will be plotted using SigmaPlot Software and the peaks of the residuals under will be identified on the plots. The logbook number for this project is CH 276.

Laboratory paper records will be maintained in accordance with Section 13.2, *Paper Laboratory Records*, of the EPA ORD Policies and Procedures Manual. The WA 3-17 WA Leaders will submit internally the raw data, including calculations and QA/QC requirements, for QA and Management review at the conclusion of each experimental run. The Pegasus QA or Technical Manager will submit the data to the EPA PI. Monthly progress reports will be submitted by Pegasus to EPA every month. Distribution of the monthly report to other agencies will be at the discretion of the EPA PI. The expected product of this research will be one final report describing the analytical results of the samples analyzed.

Records will be generated in both paper (hard copy) and electronic formats, and submitted in the format requested by the EPA PI. The following original documents generated in support of WA activities constitute records which will be managed by the Pegasus Team:

- Contract-required documents and deliverables;
- WA-specific planning documents (i.e., Work Plan and this QAPP);
- Documentation that supports fulfillment of WA-specific planning document requirements, including QA assessment reports;

Controlled access facilities that provide a suitable environment to minimize deterioration, tampering, damage, and loss will be used for the storage of records. The electronic records will be maintained on the secure network server (L:\Priv\Cin\NRMRL\TT-Group) that is backed up on a routine basis. Electronic records that are not maintained on a secure network server will be periodically backed up to a secure second source storage media, transferred to an archive media

(e.g., compact discs, optical discs, magnetic tape, or equivalent), or printed. Electronic records that are to be transferred for retention will be transferred to an archive media or printed, as directed by EPA. The EPA record schedule (501) and record retention time (permanent). The project files (electronic and non-electronic) generated under this QAPP will be retained permanently. Records will be stored at EPA Center Hill Research Facility, Lab 134 unless otherwise directed by the EPA PI who will serve as the custodian of the project records.

7. REPORTING

9.1. Periodic Reports

Monthly reports will be prepared by the Pegasus WA Leader and sent to the Pegasus On-Site Technical Manager and Project Manager, and submitted to the EPA every month. Distribution of the monthly report to other agencies will be at the discretion of the EPA PI.

9.2. Final Report

The final report will be prepared at the end of the project to summarize all the project aspects, give the final results, the conclusions and the recommendations. The report will be submitted in both hard and electronic copies. The report will be submitted to the EPA PI through the Pegasus On-Site Technical Manager; and upon approval of EPA, published as a memorandum.

8. REFERENCES

[1] http://www.epa.gov/aging/resources/presentations/2010_0112_rcra_psi_call.pdf . Accessed, August 20th, 2012.
[2] http://www.ecy.wa.gov/programs/hwtr/pharmaceuticals/pages/pu_metals.html. Accessed, August 20th, 2012.
[3] TGA 2950 Thermo gravimetric Analyzer, Operator's manual. TA Instruments, Issued July 2000, PN 925602.001 Rev.
[4] Thermal Advantage, User Reference Guide. TA Instruments, Issued July 2000, PN 9259002.002 Rev. B.
[5] http://hrc.nevada.edu/qa/ipr/ipr-035.pdf. Accessed, August 20th, 2012.
[6] ASTM (2010). Standard Practice for Calibration of Temperature Scale for Thermogravimetry, Designation E1582-10.

APPENDIX A

STANDARD OPERATING PROCEDURES

SOP 1
Weight of Residual Determination Using Sensitive Balance

1.0 Scope and Application

This procedure is designed to measure the weight of residuals in the drug containers after removing the medication.

2.0 Applicability

This procedure is applicable to AB104-S Mettler Toledo Balance located in Lab 134, CHL. The maximum weight the balance can measure is 110 grams and the minimum is 10 mg.

3.0 Sample Preservation, Containers, Handling, and Storage

- The weight of the sample will be measure immediately after receiving the necessary treatment.
- All generated wastes will be handled according to the USEPA waste management guidelines.

4.0 Equipment and Apparatus

Supplies and Equipment

- Weighing paper
- Weighing pans
- Standard Weights

Instruments

- AB104-S Mettler Toledo Balance

6.0 Procedure

- Place the weighing paper/weighing pans on the balance and tare the balance.
- Place the sample on the balance and record the weight measurement in the laboratory notebook.

7.0 Quality Assurance/Quality Control

A calibration check will be performed once before measuring the weight of the samples in a specific day. The weight calibration check is performed by measuring the weight of a calibrated mass set after taring the balance. The measured weight must fall within the tolerance of analytical balances presented in the following Table.

Tolerances for Analytical Balances

Weight	Allowed Difference Between Weight And Reading

1 g	0.1 mg
500 mg	0.1 mg
300 mg	0.1 mg
200 mg	0.1 mg
100 mg	0.1 mg
50 mg	0.1 mg
30 mg	0.1 mg
20 mg	0.1 mg
10 mg	0.1 mg
5 mg	0.1 mg
3 mg	0.1 mg
2 mg	0.1 mg
1 mg	0.1 mg

If the data does not fall within the specified limits of allowance, reject the measurements. Corrective actions will be taken to ensure the quality of the weight data. These actions will include verification of balance calibration by the NRMRL metrology lab or take balance out of service, and use an alternate balance with specifications equal to the project instrument.

SOP 2
Thermal Gravimetric Analysis (TGA)

1.0 Scope and Application

This procedure is designed to measure weight loss of samples as a function of temperature change or as a function of time at a fixed temperature.

2.0 Applicability

This procedure is applicable to TGA 2950 instrument. The TGA 2950 operates in the temperature range from ambient to 1000ºC, and has an isothermal temperature accuracy of ±1ºC and isothermal temperature precision of ±0.1ºC. It has a weighing capacity of 1.0g, a sensitivity of 0.1µg and a precision of ±0.01%.

3.0 Health and Safety

Hazards:
There is an electrocution hazard associated with the use of this equipment. The main hazards are those encountered in the use of any electrical equipment along with the following:

5. Explosion and fire caused by electrical sparks or short circuits due to open or frayed wiring.
6. The furnace and the balance chamber of the instrument are to be continuously purged with gases which require the use of pressurized gas cylinders. These gas cylinders are very heavy and unstable and can jeopardize the safety of the operator. Serious physical injuries can be result from a falling cylinder or by exposure to the full force of escaping gas. A broken valve on the cylinder can turn it into a lethal projectile. Gas pressure regulators may allow the escape of gas if not screwed tight onto the cylinders or if damaged.

Precautions:
The operator should ensure the following:

- That there is proper grounding of electrical plugs namely for the computer and the TGA 2950, etc.
- That any of the wiring is not frayed and/or open so that it comes in contact with the operator accidentally.
- That the compressed gas cylinders are appropriately stored in an upright position by using a bench-clamp or harness or a restraining chain.
- That he/she is familiar with the risks associated with the use of compressed gas cylinders.

4.0 Sample Preservation, Containers, Handling, and Storage

- No sample preservation required. The samples will be analyzed immediately.
- All generated wastes will be handled according to the USEPA waste management guidelines.

5.0 Equipment and Apparatus

Supplies and Equipment

- Brass Tweezers
- Class C calibration weight kit (1 mg to 1000 mg)
- Standard Reference Material [SRM] for temperature calibration from a qualified supplier
- Permanent bar magnet procured from a qualified supplier. (This is available as a part of the Curie calibration kit. It is noted that the above mentioned SRM are also available as part of this Curie kit)
- Platinum pans
- Conditioner Kit
- High purity Nitrogen

Instruments

TGA 2950

6.0 Procedure

6.1 Calibrating the TGA

The TGA 2950 is capable of providing several pieces of valuable information about thermal events in materials. All of the information provided (*e.g.*, weight change) is quantitative, if proper calibration is done prior to running sample materials. To obtain accurate experimental results, the TGA should be calibrated when used for the first time, and periodically thereafter.

Types of Calibration

You can access the calibration functions by choosing the desired type of calibration from the TGA **Calibrate** menu. Three types of calibration is needed for the TGA 2950: temperature, weight and sample platform calibration.

6.1.1 Taring the TGA

The **Tare** function ensures that the weight measured by the balance reflects the weight of the TGA sample only. When a pan is tared, the instrument reads the weight of the empty sample pan and then stores the weight as an offset, which is subtracted from subsequent weight measurements.

For optimum accuracy, the weight reading must be stable before it is accepted as an offset. The TGA determines when the weight reading is sufficiently stable. You should tare the sample pan before each experiment, even if you use the same pan in consecutive experiments. Taring is done for both TGA weight ranges. Tare procedure:

1. Place the empty sample pan(s) on the sample platform.
2. Select **Tare** either on the instrument keypad, by selecting **Calibrate/Tare** from the TGA menu, or by clicking on the button on the tool bar. If you are using an autosampler (AutoTGA), the **Tare Utility** window will be displayed. This allows you to specify whether you will be taring the entire platform or specific pan number(s).

6.1.2 Weight Calibration for TGA

Weight calibration should be performed on the TGA at least once a month. Because the TGA has two weight ranges, taring is done for both ranges. The tare weight is stored by the instrument for the appropriate weight range. The weight calibration functions guide you through the calibration procedure step-by step. You will need to obtain the following items for this procedure:

- two (2) empty sample pans
- calibration weights
- Brass tweezers.

NOTE: Always handle the calibration weights with brass tweezers, not with your fingers. The oils and salt from your skin can change the calibration weight.

The next several pages provide the steps needed to perform TGA weight calibration. The Instructions can also be found on the windows displayed as you step through the procedure using the *Advantage*™ program.

Step 1 of 5: Manually Tare the Balance

When you choose **Calibrate/Weight** from the TGA menu, the first window that is displayed is the **Weight Calibration - Step 1 of 5** window. Follow these steps:

1. Unscrew the tare tube in a clockwise direction, then remove it.
2. Hang an empty sample pan of the same type and size as your experimental sample pan on the tare hook. This is your tare pan.
3. Place the sample pan that you plan to use in your experiment on the sample platform.
4. Press the LOAD key on the instrument keypad to load the pan onto the sample hook.
5. Press the FURNACE key on the instrument keypad to close the furnace. Closing the furnace prevent air currents from affecting the weight reading.

Click Continue to proceed. The **Tare Stabilization** window is displayed. See "Using the Tare Stabilization Window" below for instructions.

Step 2 of 5: Zero the 100 mg Range

The **Weight Calibration - Step 2 of 5** window should now be displayed.
The instrument is now measuring the weight in the 100 mg range. The tare weight is stored by the instrument for the 100 mg range.

1. Replace the tare tube, by turning it in a counterclockwise direction to screw it back into the instrument. This will prevent air currents from affecting the weight measurement
2. Select **Continue** to go on with the calibration procedure. The **Weight Stabilization** window is displayed. See "Using the Weight Stabilization Window" for instructions.

Step 3 of 5: Zero the 1000 mg Range

The instrument is measuring the weight in the 1000 mg range. The tare weight is stored by the instrument for the 1000 mg range. Select **Continue** to go on with the calibration procedure. The **Weight Stabilization** window is displayed. See "Using the Weight Stabilization Window" for instructions.

Step 4 of 5: Calibrate the 100 mg Range

This step in the procedure calibrates the 100 mg weight range for the TGA instrument.

1. Obtain the 100 mg class M standard weight from the TGA Accessory Kit.
2. Place the 100 mg weight in the sample pan.
3. Select LOAD to load the pan onto the sample hook.
4. Press the FURNACE key to close the furnace. Closing the furnace prevent air currents from affecting the weight reading.

Enter the exact mass of the standard as seen on the TGA display (default value =100.0 mg), then select **Continue**. The system will begin measuring the combined weight of the standard and the pan. The **Weight Stabilization** window is displayed.

Step 5 of 5: Calibrate the 1000 mg Range

This step in the procedure calibrates the 1000 mg weight range for the TGA instrument.

1. Obtain the 1000 mg class M standard weight from the TGA Accessory Kit.
2. Select UNLOAD to unload the sample pan and remove the 100 mg weight.
3. Place the 1000 mg weight in the sample pan.

4. Select LOAD to load the pan onto the sample hook.
5. Enter the exact mass of the standard as seen on the TGA display (default value = 1000.0 mg), then select **Continue**. The system will begin measuring the combined weight of the standard and the pan. The **Weight Stabilization** window is displayed. Once the weight reading is close to 1000 mg (+ 50 mg), then press the FURNACE key to close the furnace and stabilize the weight. See "Using the Weight Stabilization Window" on the previous page for instructions. After you accept the weight, the calibration is complete.
6. Unload the sample pan.

6.1.3 Adjusting the TGA Sample Platform

The Sample Platform Adjust procedure is used if the sample hang-down wire fails to pick up a sample pan during an automatic loading procedure. The sample platform must be adjusted so that the instrument can properly load and unload the sample pans.
To avoid weight signal noise, the TGA must be level so that the sample pan and hangdown- wire hang inside the furnace and thermocouple tube without touching them. The first step of the sample platform calibration procedure adjusts and levels the instrument.
Select **Calibrate/Platform** from the TGA menu. The first window in a step-by-step series of instructions is displayed. The next several pages provide the steps needed to perform TGA sample platform calibration. The instructions can also be found on the windows displayed as you step through the procedure using the *Advantage*™ program.

NOTE: The sample platform adjustment procedure is slightly different for the TGA Autosampler, turn to page 2-70 for those instructions.

Step 1: Center the Sample Pan

In order to center the sample pan, the top and bottom of the sample hang-down wire must be adjusted and the instrument leveled. When you choose **Calibrate/Platform** from the TGA menu, the **Platform Adjust**

Step 1 window is displayed.
1. Load an empty sample pan on the instrument balance (it can be done automatically or manually).
2. Check to see whether the top end of the sample hang-down wire is hanging freely and roughly centered within the top of the thermocouple tube inside the balance chamber.
If the wire is not roughly centered, turn the balance adjustment screw until the wire is centered.
3. Raise the furnace just to the bottom of the sample pan.
4. Check the alignment of the sample pan within the furnace. It should hang freely, roughly centered, and should not be touching the sides of the furnace or the hangdown-tube. If the pan is not centered, adjust the feet on the bottom of the instrument until the pan hangs correctly. Turn the feet clockwise to lengthen or counterclockwise to shorten the instrument leveling feet.
5. Select **Continue** to go on with the calibration procedure.

Step 2: Platform Arm Positioning

The **Platform Adjust - Step 2** window should now be displayed. Once the sample pan has been centered over the furnace, you will need to adjust the position of the platform arm so that the pans can load and unload correctly.

• You can enter the number of units that you want to move the platform in the box on the left side of the window, or
• You can use the slide bar to change the platform position by: (a) clicking on the appropriate load direction button to move the platform one unit at a time, (b) clicking in the slider shaft to move the platform five units for each click, or (c) placing the cursor on the slider and holding the mouse button down as you slide it in the desired direction.

Select the **Test Position** button to move the platform arm to the selected position, and then select **Continue** to go on with the calibration procedure.

Step 3: Manual Platform Adjustment

The **Platform Adjust - Step 3** window should now be displayed.

1. Use a screwdriver to loosen the set screw located under the sample platform.
2. Move the sample platform: (a) rotate it until the sample holder is directly under the pan, then (b) adjust the height of the platform until the bottom of the pan is located approximately 1 mm above the platform.
3. Use the screwdriver to tighten the setscrew again (do not overtighten as you may strip the threads).
4. Rotate the sample pan holder until the groove in the pan hole aligns with the wire on the bottom of the sample pan.
5. Select **Done** when these steps have been accomplished. The Sample Platform Adjustment has been completed.

6.1.4 Adjusting the AutoTGA Sample Platform

The Sample Platform Adjust procedure is used if the sample hang-down wire fails to pick up a sample pan during an automatic loading procedure. The Autosampler sample platform must be adjusted so that the instrument can properly load and unload the sample pans.

To avoid weight signal noise, the TGA must be level so that the sample pan and hangdown wire hang inside the furnace and thermocouple tube without touching them. The first step of the sample platform calibration procedure adjusts and levels the instrument.

Select **Calibrate/Platform** from the AutoTGA menu. The first window in a step-by-step series of instructions is displayed. The next several pages provide the steps needed to perform the AutoTGA sample platform calibration. The instructions can also be found on the windows displayed as you step through the procedure using the *Advantage* program.

Step 1: Center the Sample Pan

In order to center the sample pan, the top and bottom of the sample hang-down wire must be adjusted and the instrument leveled. When you choose **Calibrate/Platform** from the TGA menu, the **Platform Adjust Step 1** window is displayed.

1. Load an empty sample pan on the instrument balance (it can be done automatically or manually).
2. Check to see whether the top end of the sample hang-down wire is hanging freely and roughly centered within the top of the thermocouple tube inside the balance chamber.

If the wire is not roughly centered, turn the balance adjustment screw until the wire is centered.

3. Raise the furnace just to the bottom of the sample pan.
4. Check the alignment of the sample pan within the furnace. It should hang freely, roughly centered, and should not be touching the sides of the furnace or the hang down tube. If the pan is

not centered, adjust the feet on the bottom of the instrument until the pan hangs correctly. Turn the feet clockwise to lengthen or counterclockwise to shorten the instrument leveling feet.
5. Select **Continue** to go on with the calibration procedure.

Step 2: Manual Platform Height Adjustment

The **Platform Adjust - Step 2** window should now be displayed.
After the sample pan has been centered in step 1, the height of the platform must be manually adjusted as follows:
1. Use a screwdriver to loosen the setscrew located in the platform hub.
2. Move the sample platform: (a) rotate the hub and platform until the sample holder is directly under the pan, then (b) adjust the height of the hub and platform until the bottom of the pan is located approximately 1 mm above the platform.
3. Use the screwdriver to tighten the setscrew again (do not overtighten as you may strip the threads).
4. Select Continue to go on with the calibration procedure.

Step 3: Manual Sample Arm Length Adjustment

The **Platform Adjust - Step 3** window should now be displayed. The length of the autosampler arm must now be adjusted to allow proper pickup of the samples.
1. Use a screwdriver to loosen the two setscrews located on the sample arm.
2. Move the sample arm to adjust the position of the groove: (a) move the sample arm OUT to make the sample holder groove rotate clockwise, or (b) move the sample arm IN to make the sample holder groove rotate counterclockwise. When the groove aligns with the wire bale on the bottom of the pan, go on to the next step.
3. Use the screwdriver to tighten the two setscrews on the sample arm.
4. Select **Continue** to go on with the calibration procedure.

Step 4: Platform Arm Positioning

NOTE: There may be a slight delay while the instrument initializes to prepare for this step. The window controls will be disabled until this operation has been completed.
The **Platform Adjust -Step 4** window should now be displayed.
Once the sample pan has been centered over the furnace, you will need to adjust the position and rotation of the platform arm so that the pans can load and unload correctly.
• You can enter the number of units that you want to move the platform, in the box on the left side of the position or rotation slide bar. or
• You can use the slide bar to change the platform position and rotation by: (a) clicking on the appropriate direction button to move the platform one unit at a time, (b) clicking in the slider shaft to move the platform five units for each click, or (c) placing the cursor on the slider and holding the mouse button down as you slide it in the desired direction.
Select the **Test Position** button to move the platform arm to the selected position and rotation, then select **Done** when you are satisfied that the platform arm is in the correct position.

6.1.5 Temperature Calibration for the TGA

Temperature calibration is useful for experiments in which precise transition temperatures are essential. To temperature calibrate the TGA, first you need to analyze a high-purity metal for its curie temperature, and then enter the observed and correct values in the temperature calibration table.
NOTE: The Temperature Calibration Table is not available when the instrument is in the calibration mode.

Before you can perform the temperature calibration procedure for the TGA, you must first reset the **Temperature Calibration Table** as follows: 1. Select **Calibrate/ Temperature** from the TGA menu. The **Temperature Table** is displayed.
2. Click the **Reset** button to reset all temperature calibration data before performing any new calibration experiments.
3. Click OK.
4. Gather the calibration data by following the steps on the next page to determine the curie temperature.
5. Perform the temperature calibration as directed on the next page

Determining Curie temperature

A general procedure for Curie temperature calibration is given below.
1. Choose standards that encompass your experimental range. Multiple standards may be needed for this purpose. Choose standards whose curie temperature differs substantially; each pair of curie temperatures must differ from all other pairs by at least 10°C.
2. Place the curie temperature sample in a tared TGA sample pan and position the pan on the sample platform.
3. Select the **Experiment View**. Enter the requested sample information, including name on the **Summary Page**. Select the Ramp test from the Test list.
4. Click on the **Procedure Page**. Enter the requested test parameters that will program the TGA to: (a) equilibrate to 100°C below the onset of the literature curie temperature of your material, and (b) heat the material, at the same heating rate that you will use in your experiments, to above the literature curie temperature.
5. Click on the **Notes Page**. Enter/verify the requested information.
6. Click on the **Apply** button to save the experimental and sample parameters entered for this run. If more than one run is in the sequence list, schedule this run (will appear next to the run number in the **Sequence Pane** for the scheduled run)
7. Start the method and observe Signal A (weight loss %) on the **Signal Display Pane**.
8. Slowly raise the magnet under the furnace until a weight gain (< 2%) is detected. Secure the magnet in this position for the duration of the experiment.
9. Determine the curie temperature by analyzing the extrapolated end point of the Sshaped curve using the data analysis program.
10. Enter the Observed and Correct temperatures in the Temperature table when all the experiments are complete as directed in the next section.

Enter the Temperature Calibration

1. Select **Calibrate/Temperature** from the TGA menu. The **Temperature Table** is displayed. This window shows the temperature calibration table that the instrument applies to the collected data. Use this window to enter from one to five temperature calibration points (pairs of observed and correct temperature points). The observed and correct temperature corresponds to the experimental and theoretical transition temperature (*e.g.*, melting point) of the calibrant respectively.
2. If these values are correct, select OK.

If new values are to be entered:
a. Enter the Observed and Correct temperature points in the table.
b. Select OK when all points have been entered to save the settings to the instrument.

6.2 Running TGA for Samples

The following steps will be followed to analyze a sample on TGA:

- Select the pan type and material
- Load the pan
- Tare the empty sample pan
- Load the sample into the pan
- Enter the experimental information through the TGA controller (sample and instrument information)
- Create and select the thermal method on the controller
- Attach and set up accessories as required (e.g., purge gas)
- Start the experimental run

7.0 Quality Assurance/Quality Control

A calibration check should be performed after the weight and temperature calibrations have been completed. After the temperature calibration check is performed, the 'observed' curie transition temperature must fall within ± 5°C of the limits for SRM standards. The weight calibration check is performed by placing a known weight from the calibrated mass set into the sample pan. The 'observed' weight must fall within the tolerance of analytical balance presented in the following Table.

Tolerances for Analytical Balances

Weight	Allowed Difference Between Weight And Reading
1 g	0.1 mg
500 mg	0.1 mg
300 mg	0.1 mg
200 mg	0.1 mg
100 mg	0.1 mg
50 mg	0.1 mg
30 mg	0.1 mg
20 mg	0.1 mg
10 mg	0.1 mg

5 mg	0.1 mg
3 mg	0.1 mg
2 mg	0.1 mg
1 mg	0.1 mg

If the data does not fall within the specified limits of allowance, reject the measurements. Perform the weight and temperature calibration again before performing any experiments for data collection. If the calibration is rejected, re-calibrate the instrument and perform the calibration check until the instrument is accepted to be in calibration. If the instrument cannot be calibrated, contact the manufacturer to get it adjusted. Perform an additional calibration for verification.

8.0 References

TGA 2950 Thermo gravimetric Analyzer, Operator's manual. TA Instruments, Issued July 2000, PN 925602.001 Rev.
Thermal Advantage, User Reference Guide. TA Instruments, Issued July 2000, PN 9259002.002 Rev. B.
ASTM (2010). Standard Practice for Calibration of Temperature Scale for Thermogravimetry, Designation E1582-10.

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12 Appendix E

Date: October 31, 2014
To: Thabet Tolaymat, EPA ORD
From: Keith Weitz
Subject: Peer Review Comments Summary – Evaluation of P-Listed Pharmaceutical Residues in Empty Pharmaceutical Containers

Task 6 of WA 3-05, *Material Management Research*, called for an external peer review of the EPA report *Evaluation of P-Listed Pharmaceutical Residues in Empty Pharmaceutical Containers*. Under the Resource Conservation and Recovery Act (RCRA), some pharmaceuticals are considered acute hazardous wastes because their sole active pharmaceutical ingredients are "P-listed commercial chemical products". Hospitals and healthcare facilities have struggled with RCRA's empty container requirements when it comes to disposing of visually empty warfarin and nicotine containers, and this report was prepared to investigate the issue. EPA's Office of Resource Conservation and Recovery asked EPA's Office of Research and Development to conduct research to evaluate the differences in pharmaceutical residues between triple rinsed P-listed pharmaceutical containers and those that were not treated.

Specifically, nicotine gums, patches and lozenges are considered to be hazardous wastes because nicotine and its salts are listed as EPA Waste No. P075, and Coumadin (also known as warfarin) is hazardous because warfarin and its salts are listed as EPA Waste No. P001 (when warfarin is present at concentrations greater than 0.3%). Therefore, when unused nicotine-based smoking cessation products (e.g., patches, gums and lozenges) and Coumadin are discarded, they are regarded as acute hazardous wastes and must be managed in accordance with all applicable RCRA regulations. Furthermore, due to additional management requirements for P-listed wastes, any acute hazardous waste residues remaining in containers (and therefore the container itself) must be managed as hazardous unless the container has been rendered "RCRA empty" either by triple-rinsing with an appropriate solvent or by another method proven to achieve equivalent removal.

In this memorandum, peer review comments received per the subject report are summarized. Comments are summarized based on the pre-defined (by EPA) peer review charge questions:

1. Barring direct analysis of the active pharmaceutical ingredient, is the methodology followed in this report sufficient to answer the research question posed?
2. Overall, are the presented data accurate enough to answer the research question?
3. Do the data collected in this study support the conclusion of the report?

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Reviewer comments as received, and organized by peer review charge question are included in Attachment A.

Peer Review Panel

Peer reviewers engaged for this assignment were selected based on RTI expertise and recommendations obtained from the research community. They were evaluated by RTI to ensure that they met qualifications according to the *EPA Peer Review Handbook*. Reviewers included the following individuals:

- **Shannon Bartelt-Hunt**, University of Nebraska, College of Engineering—Ph.D. and M.S. in Civil Engineering (Environmental), University of Virginia; B.S. in Environmental Engineering, Northwestern University. Ms. Bartelt-Hunt has expertise in numerical and experimental investigations of contaminant transport in natural and engineered systems, fate and transport of emerging contaminants, design of remediation systems for contaminated soil and groundwater, design of barrier systems for waste disposal applications.
- **Jon Powell**, Innovative Waste Consulting Services—B.S. in Environmental Engineering Sciences and a Master of Engineering in Environmental Engineering Sciences from the University of Florida. Mr. Powell is a Professional Engineer with broad expertise in waste and materials management, with work spanning waste facility operations, design, applied research, and training.
- **Jennifer Redmon**, RTI International—Master of Science and Environmental Science in Environmental Chemistry, Toxicology and Risk Assessment, Indiana University; Master of Public Affairs in Environmental Policy and Natural Resource Management, Indiana University; B.S. in Public Affairs in Environmental Management, Indiana University. Ms. Redmon is an environmental scientist and risk assessor with dual graduate degrees that provide her with a multi-faceted background in environmental chemistry, toxicology, risk assessment, environmental policy and natural resource management. Ms. Redmon is also a certified hazardous materials manager.

Is the Methodology Sufficient to Answer the Research Question Posed?

1) Reviewers understood the basic research question to be "Is there a difference between triple-rinsed P-listed pharmaceutical containers and those that are not triple-rinsed?" Reviewers commented that a clear statement of this research question in the executive summary would be helpful and provide necessary context when results are discussed.

Response:

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The research question is clearly stated in the executive summary of the revised report as follows *"The primary objective of the current study was to answer the research question "Is there a difference between empty P-listed pharmaceutical containers that are triple-rinsed and those that are not triple-rinsed?" The study objective was accomplished via two tasks: 1) calculating the "maximum possible weight of residual drug/total residual /container" for each compound and packaging combination to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container and 2) evaluating, qualitatively, the presence of active pharmaceutical ingredient in the residues. The experimental test program included the use of a sensitive balance to determine the total amount of residues in the empty pharmaceutical containers and a thermal gravimetric analysis to qualitatively evaluate the presence of the active pharmaceutical compounds in the residues. The P-listed pharmaceuticals evaluated in the study were nicotine, Coumadin, and physostigmine."*

2) To investigate the research question posed, actual P-listed containers were obtained and emptied in a way that simulated actual use. Then, the empty containers were either not treated (not rinsed); single triple rinse with DI water, or a double triple rinse with methanol to serve as a negative control. The amount of residue (specifically nicotine, Coumadin, and physostigmine) in each container was determined using a sensitive balance. The difference in weight between the untreated and treated containers was attributed to any remaining residual. After weighing, the residual was swabbed with a cotton swab and subjected to thermal gravimetric analysis (TGA) to qualitatively identify the active pharmaceutical ingredient.

Response:

The above mentioned statement, "The amount of residue (specifically nicotine, Coumadin, and physostigmine) in each container was determined using a sensitive balance", does not accurately represent the role of the sensitive balance in the study. The balance was used for determining the total amount of residues in the empty containers and not for determining the fraction of nicotine, Coumadin, and physostigmine (if any) in the residues. The total amount of residues determined using the balance along with information from the drug manufacturers were then used to infer an upper limit for the amount of active pharmaceutical compound in the total residue in the containers. In summary, to accurately represent the work conducted in the study "The total amount of residues including the active pharmaceutical ingredient was determined using a sensitive balance" is more accurate representation than "The amount of residue (specifically nicotine, Coumadin, and physostigmine) in each container was determined using a sensitive balance."

3) For tablet or other non-liquid medications, all reviewers did not think the methodology used was sufficient to answer the research question, which was determining the amount of active pharmaceutical residual in each container. Reviewers commented that the use of the balance is sufficient to determine the amount of the residual, but there is likely an uneven distribution of the active ingredient in the tablet formulation. The report indicates that the coating or outer layer of the medication likely does not contain the active ingredient. Reviewers thought it likely that the residual in these containers is predominantly from the coating or outer layer of the medication. It is not clear if the residual remaining in these containers contains the active ingredient or not, as

the TGA analysis was inconclusive. In addition, reviewers noted that no active ingredient was detected in any of the TGA analyses.

Response:

As mentioned in section 3 of the report, the objective of the study was not to determine the actual amount of active pharmaceuticals in the residues. Rather, the tasks were to: 1) determine the total amount of residues (using sensitive balance); 2) infer upper limit for the amount of active ingredient in the residues using the data collected from task 1; and 3) qualitatively evaluate the presence of the active pharmaceutical ingredients in the residues (using TGA). We agree with the reviewers that the data presented for solid medication in this report do not quantify the amount of the active pharmaceutical compounds in the residues of each container. However, the study objectives (stated in section 3) did not include quantitative determination of the amount of active ingredients and further work is warranted using other analytical techniques in order to quantitatively determine the amount of the active pharmaceutical ingredients. To clarify this point, the following was added to the executive summary and conclusion sections in the revised report "For medication in solid form (i.e., tablet, gum, and lozenge) and patches, there was no difference between triple-rinsed containers and those that are not triple-rinsed. However, this conclusion is based on a qualitative analysis by TGA which is limited by the TGA sensitivity. Other analytical techniques are needed to verify the TGA results for these medications and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any)."

Furthermore, the TGA results and balance results should be considered collectively rather than individually when analyzing the data and drawing conclusions. Analyzing the results in this context makes the TGA results more meaningful. Thanks to the reviewers' comment, this important point was clarified through examples in the revised conclusion section of the report as follows:

- *The nicotine nasal spray 10 mg/ml was the only medication to have positive TGA results (active pharmaceutical drug was detected in the residuals) as the residues had a $T_{max\ wt\ loss}$ at 217 ^{o}C that is representative of nicotine. But the $T_{max\ wt\ loss}$ for the negative control (cotton piece) was shifted in this case (as mentioned in the report the shift is not because of any issues with the calibration) which may be attributed to a reaction between the residual liquid and the cotton piece that caused changes in the properties of the cotton piece. Nonetheless, the fact that this medication is in liquid from and contains 67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ^{o}C represent nicotine.*
- *For the blister packs and nicotine patches, the calculated upper limit for the amount of active pharmaceutical compound in the total residue was relatively low and ranged from 0 to 8 µg. These amounts are upper limit and the actual amounts of active compounds in the residues are more than likely lower because the outer layer of the medication acts as a coating to prevent the loss of the drug until the medication reaches the target location*

in the body and thus, this layer does not probably contain the drug. The balance and upper limit results support the TGA results which were negative for these pharmaceutical packages.

- *For the plastic containers encompassing warfarin tablets (1, 5, and 10 mg), detectable quantities of residues were found in the empty containers. The TGA results for the same containers showed clear peaks for these residues, however, the peaks did not correspond to the warfarin and thus, they most likely represent the coating materials. These data support the aforementioned assumption that the residues in these cases are mainly composed of coating materials. Nonetheless, having negative TGA results do not eliminate the possibility of the presence of the active pharmaceutical compound in the residues but if it is present it represent a relatively small fraction.*
- *The aforementioned conclusions highlight the importance of considering the balance results and TGA results collectively rather than individually when analyzing the data.*

4) For liquid medicines, all reviewers did think the methodology of weighing the residual was sufficient to answer the research question for the case of liquid medicines. In this case, the residual is known to contain the active ingredient, since the active ingredient is likely to be more homogeneously distributed throughout the medication. A) One reviewer questioned whether this is true for all liquid medicines, commenting that many require agitation (shaking) prior to use. Reviewers noted that by using the manufacturer's information regarding the percentage of the active ingredient, and the amount of residual measured, the amount of pharmaceutically-active residual can be determined. B) Despite this, reviewers found the results somewhat troubling in that the TGA analysis did not detect any of the active pharmaceutical ingredients in the liquid medications. Reviewers felt this may be due to the sensitivity of balance used for the TGA analysis, which was not directly discussed in the report.

Response:

A) This is true for all liquid medications tested because of two reasons: 1) the tested liquid mediations were solutions (not suspensions) and 2) there was no mentioning on the drug package of a requirement or recommendation to shake the medication before use. A note of that is included in section 7 in the revised report.
B) The following information was included in the revised report (sections 5.4.10 and 7) in the response to the comment: "All TGA results were negative (no active pharmaceutical drug was detected in the residuals) except for the nicotine nasal spray 10 mg/ml which had a $T_{max\ wt\ loss}$ at 217 ^oC that is representative of nicotine. It should be noted that $T_{max\ wt\ loss}$ for the negative control (cotton piece) was shifted in this case which may be attributed to a reaction between the residual liquid and the cotton piece which may have resulted in changes in the properties of the cotton piece. Nonetheless, the fact that this medication is in liquid from and contains 67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ^oC represent nicotine."

5) One reviewer suggested that some type of statistical treatment on the quantitative results could be warranted. A 'readability' of 0.1 mg is important in this study because the differences for some of the drugs tested were very close to this value – this fact, coupled with a lack of statistical treatment, makes it difficult to conclude that a residue was present. Another comment questioned data accuracy relating to some of the reported masses and significant figures. Specifically, many of the results were reported to several decimal places (e.g., 0.3000 mg on page 25) and the reviewer felt that readers are left to wonder how data could be reported that way of the readable limit of the scale was 0.1 mg.

Response:

I would appreciate if the reviewers clarify what is meant by "lack of statistical treatment".

We do apologize for reporting some of the results with zeroes to fill decimal places that should not be there. Throughout the report, all the extra zeroes were deleted for the total amount of residuals that were experimentally determined by the balance.

6) Another reviewer commented that it would be useful if additional detail was presented in the Methodological Approach (Section 4.0) explaining differences in the package types and justifying why the chosen analytical methods were deemed optimal for the given study, potential limitations, and comparison to other considered approaches. The study results suggest that the sensitive balance was not sensitive enough to detect mass balance changes in all packages before and after drug removal, and therefore the drug residue and active pharmaceutical amounts could not be accurately quantified for all drugs, even when active pharmaceutical drug may have been detected in the TGA results for the same sample. Additionally, Experimental Steps (Section 4.2) notes that foil wrap packaging was not tested for plastic wrap peel offs, but does not provide justification for this decision. The study results later suggest that samples with plastic wrap peel contain no residual (within the range of the error of the balance), but the data appear suspect because a portion of the packaging was not tested to confirm that it did not contain drug residual.

Response:

We added a table (Table 1 in the revised report) to the methodology section that includes additional details regarding the investigated medications, doses, and types of packages.

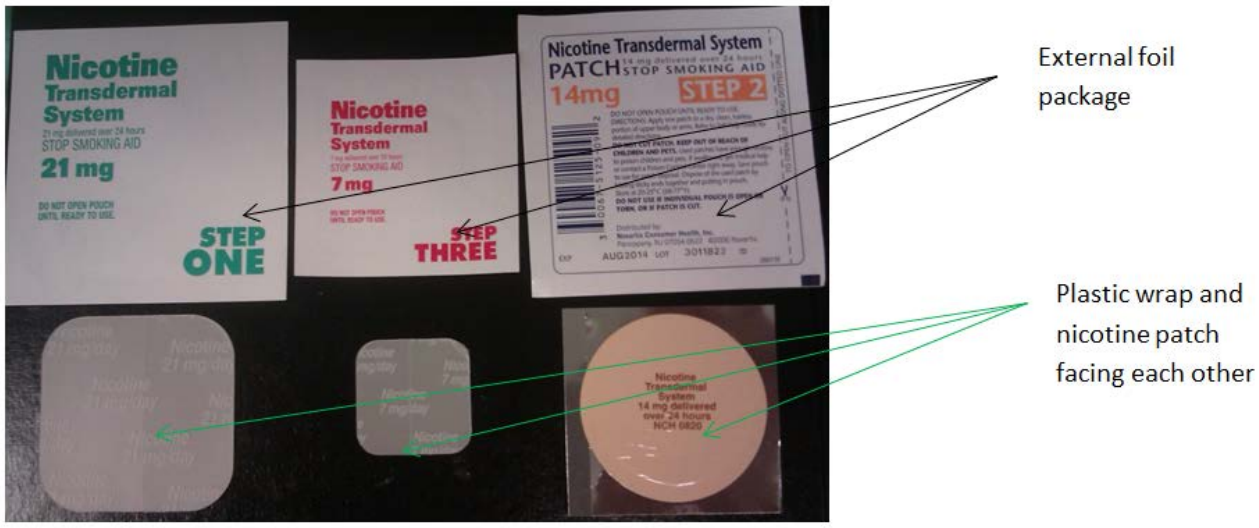
Table 31. List of medications and package types

Medication	***Form and Dose***	***Package Type***
Warfarin	*Warfarin sodium tablets, 1 mg*	*Plastic container*
	Warfarin sodium tablets, 5 mg	*Plastic container*
	Warfarin sodium tablets, 10 mg	*Plastic container*
	Warfarin sodium tablets, 2 mg	*Blister pack*
	Jantoven tablets, 1 mg	*Blister pack*
	Jantoven tablets, 10 mg	*Blister pack*
Nicotine	*Nicorette gum, 2 mg*	*Blister pack*
	Nicorette gum, 4 mg	*Blister pack*
	Nicotine polacrilex gum, 2 mg	*Blister pack*

Medication	***Form and Dose***	***Package Type***
	Nicotine polacrilex gum, 4 mg	*Blister pack*
	Nicorette mini lozenge, 2 mg	*Plastic container*
	Nicorette lozenge, 4 mg	*Plastic container*
	Nicotine transdermal patch, 7 mg	*Plastic wrap (peel off) enclosed in foil wrap*
	Nicotine transdermal patch, 14 mg	*Plastic wrap (peel off) enclosed in foil wrap*
	Nicotine transdermal patch, 21 mg	*Plastic wrap (peel off) enclosed in foil wrap*
	Nicotrol nasal spray, 10 mg/ml	*Glass vial*
	Nicotine inhaler, 10 mg/cartridge	*Plastic container*
Physostigmine Salicylate	*Physostig-mine salicylate, 1 mg/ml*	*Glass ampule*

The revised conclusion section in the report presented the limitations of the analysis and interpretation of the results in light of the limitations (please refer to section 7 in the revised report). As indicated in section 7, the medications packaged in blister packs and plastic wraps contained minimal residuals, in the range of the error of the balance used in the study, after removing the drugs. Although the sensitivity of the balance did not allow for determining the actual amount of total residues in these package types, the results infer an upper limit for the total amount of residues in these packages.

For the nicotine patches, the picture presented below shows that the nicotine patch faces a plastic wrap and both are enclosed in an external foil type package. The active side of the nicotine patch is only in contact with the plastic wrap that is facing it and securing it from releasing the drug to other surfaces. The drug can only release when the internal plastic wrap is peeled off. Therefore, the external foil package will not contain residues as it is not in contact with the patch and that is the reason for not conducting any experimental testing on it. The following information is added to the revised report (section 4.2) to clarify this point "The external foil wrap packaging was not tested because the active side of the nicotine patch is only in contact with the plastic wrap that is facing it and securing it from releasing the drug to other surfaces. The drug can only release when the internal plastic wrap is peeled off. Therefore, the external foil package will not contain residues as it is not in contact with the patch and therefore it was not experimentally tested."



Are Data Accurate Enough to Answer the Research Question?

8) In general, all reviewers agreed that the study methods proposed were sound and allowed for the collection and analysis of data regarding the question of whether there is residual contained in the discarded packaging via sensitive balance. Reviewers believed the weight data on residual are accurate enough to determine the amount of residual in the container. The mass results show a downward trend for most of the different containers (non-blister packs) as more rinsing was done, which is expected if there is residue present. So this observation appears to be effective in terms of accuracy to help answer the research question.

Response:

Thank you.

8) However, the reviewers did not think that the data are accurate enough to determine whether the residual contained the active pharmaceutical ingredient. One reviewer commented that the report doesn't include the minimum level of detection of the active ingredients by TGA. Because no active ingredients were detected using TGA, the reviewer noted that it is not clear whether no active ingredients were present, or if the TGA was not sensitive enough to detect the small amount of active ingredient in the sample. Another reviewer noted that drugs showing a mass difference in residuals at the 1 or 10-mg level are clear and scale readability may not matter in those cases.

Response:

As pointed out in response to comment 3, the TGA results and balance results should be considered collectively rather than individually when analyzing the data and drawing conclusions. Analyzing the results in this context makes the TGA results more meaningful despite the limitation of sensitivity of TGA in some of the investigated cases. For example, for the blister

packs and nicotine patches, the calculated upper limit for the amount of active pharmaceutical compound in the total residue was relatively low and ranged from 0 to 8 µg. These amounts are upper limit and the actual amounts of active compounds in the residues are more than likely lower because the outer layer of the medication acts as a coating to prevent the loss of the drug until the medication reaches the target location in the body. Thus, residues my not contain the drug. The balance and upper limit results support the TGA results which were negative for these pharmaceutical packages. Another example of using TGA and balance data collectively was the case of nicotine nasal spray 10 mg/ml which was the only medication to have positive TGA results (active pharmaceutical drug was detected in the residuals). For this medication, the residues had a $T_{max\ wt\ loss}$ at 217 ^oC that is representative of nicotine. But the $T_{max\ wt\ loss}$ for the negative control (cotton piece) was shifted in this case (as mentioned in the report the shift is not because of any issues with the calibration) which may be attributed to a reaction between the residual liquid and the cotton piece that caused changes in the properties of the cotton piece. Nonetheless, the fact that this medication is in liquid from and contains 67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ^oC represent nicotine.

The following information was included in the revised conclusion section (section 7 in the revised report) along with a table (Table 6) that summarizes the results and highlights the limitation of analysis on a case by cases basis. This information clearly states the cases that had conclusive results from the cases that had constraints because of sensitivity of equipment used in the study.

- *"For the medications in liquid form (Nicotrol nasal spray 10 mg/ml and Physostigmine salicylate 1 mg/ml), there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not triple-rinsed containers contain the active pharmaceutical ingredient.*
- *For Nicotine inhaler 10 mg/cartridge, there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not triple-rinsed containers contain the active pharmaceutical ingredient.*
- *For medication in solid form (i.e., tablet, gum, and lozenge) and patches, the TGA results showed no difference between triple-rinsed containers and those that are not triple-rinsed. However, this conclusion is based on a qualitative analysis by TGA that is limited by the TGA sensitivity. Other analytical techniques (e.g., gas chromatography or liquid chromatography equipped with mass spectrometer) are needed to verify the TGA results for these medications and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any)."*

With regards to the comment on determining the TGA sensitivity: it was practically difficult to accurately determine the TGA sensitivity for the tested pure compounds. The major reason for this difficulty was that the pure compounds were treated as samples (the pure compounds had to be loaded on a cotton piece) and there was no control over how much sample was exactly loaded on the cotton piece especially that these samples were tested in fume hood (for safety reasons) and a fraction of the sample may be lost during loading because of the air current in the hood.

9) One reviewer commented that the QA/QC data appear to suggest that tolerance limits of different instruments were met. However, the reviewer noted instances where neither of these methods are sufficient for data evaluation either due to method constraints (e.g. sensitive balance), a need for additional QC (e.g. TGA data), or other uncertainties and study limitations that are not thoroughly discussed in the report at this time. The reviewer detailed the key concerns associated with the sensitive balance and TGA data as follows:

- A) Sensitive Balance Data – The sensitive balance was not sensitive enough to detect mass balance changes in all packages before and after drug removal, and therefore the drug residue and active pharmaceutical amounts could not be accurately quantified for those drugs, even when active pharmaceutical drug may have been detected in the TGA results for the same sample. Additionally, samples with plastic wrap peel were deemed to contain no residual (within the range of the error of the balance), but a portion of the packaging was not tested to confirm that it did not contain drug residual, and these peel offs are lower in mass, and thereby more likely to be constrained by study method limitations given that the smallest readable balance measurement was 0.1 mg. Therefore, certain packaging types may not be suitable for testing with the balance used during the testing. Perhaps a more sensitive balance could at least be secondarily used in cases where either 1) TGA results reveal active pharmaceutical ingredients while the balance does not indicate that there is residuals, or 2) the packaging is constructed of lower weight material (e.g. peel offs).

  <u>Response:</u>

- *As previously mentioned in response to comment 6, the revised conclusion section in the report presented the limitations of the analysis and interpretation of the results in light of the limitations (please refer to section 7 in the revised report). Section 7 in the revised report include the following "the medications packaged in blister packs and plastic wraps contained minimal residuals, in the range of the error of the balance used in the study, after removing the drugs. Although the sensitivity of the balance did not allow for determining the actual amount of total residues in these package types, the results infer an upper limit for the total amount of residues in these packages." For the nicotine patches, the picture presented in response to comment 6 showed that the nicotine patch faces a plastic wrap and both are enclosed in an external foil type package. The active side of the nicotine patch is only in contact with the plastic wrap that is facing it and securing it from releasing the drug to other surfaces. The drug can only release when the internal plastic wrap is peeled off. Therefore, the external foil package will not contain residues as it is not in contact with the patch and that is the reason for not conducting experimental testing on it. With regards to the use of more sensitive balance for the cases where the residues were in the range of the error of the balance: we agree that it is a*

good measure to use a more sensitive balance in these cases, however, we did not have access to such balance. Nonetheless, as stated above, although the sensitivity of the balance did not allow for determining the actual amount of total residues in these package types, the results infer an upper limit for the total amount of residues in these packages.

- B) TGA Data – A full product listing in the main body of the report and an additional QC of the final number of medications and a summary of TGA failures is needed. In Section 6.3, the authors should note which 4 drug products failed the TGA test to allow for optimal transparency. The reader has to sift through the whole report to find which products fail in the current version of the report. Furthermore, this section notes that 17 medications were tested, but the QAPP and Section 7 Conclusions notes that a different number were tested (18 in conclusions, and 19 in the QAPP).

  Response:

- *A full product listing was included in Table 1 in the main body of the revised report; please refer to section 4.1 in the report. The tests that did not meet the DOQ for TGA were specified below Table 5 in the revised report. The total number of medications included in the study was18. One medication (nicotine inhaler) out of the 18 was not tested experimentally because the actual amount of active pharmaceutical compound in the residue was determined through information provided by the manufacturer (please review section 5.4.11 in the report). Therefore 17 medications were experimentally tested in the study. To clarify this point, the word "experimentally" was included in the phrase in section 6.3 as follows "17 medications experimentally tested".*

Do Data Collected Support the Conclusions of the Research?

Reviewers generally agreed that the data collected in the study do support the conclusion of the report that all plastic containers used for medications and evaluated in this study contained residuals, but that the amount of active pharmaceutical ingredients in the residual could not be determined. Reviewers also generally agreed with the conclusions regarding the liquid drugs, as the active ingredient should be homogeneously distributed throughout the medication.

However, reviewers also felt that the results do not sufficiently answer the overall research question, which was to determine the difference in the amount of pharmaceutically-active ingredient in the rinsed and non-rinsed containers. Reviewers felt that this question could not be answered because the amount of pharmaceutically-active ingredient (or even the presence of the active ingredient) could not be determined using the methods employed.
Reviewers also noted that the report contained inconsistent characterizations of the results. For example, the executive summary of the report highlights that the qualitative TGA results show

that there is "no observable difference [in the presence of active ingredients] between containers that were triple rinsed and containers that were not" except for nicotine nasal spray. However, the conclusions (Section 7) states that all medications in plastic containers contain measurable residual levels, but it was not possible to determine the amount of active pharmaceutical ingredients using TGA. Furthermore, the conclusions section does not discuss the nasal spray results at all.

One reviewer recommended that a step-wise summary of the report findings is necessary to come to a final conclusion on whether or not there is a difference between triple rinsing for some pharmaceutical-package combinations. Specifically, the individual package type or drug results are not summarized in a consistent and thorough manner. Adding a summary table would be a very useful way to review the drug, dose, product, and package types evaluated along with at least qualitative information on whether the TGA results were positive (indicating active drug residual was present in discarded packaging), along with the measured residual weight (binned into weight ranges, or with the average value), and the theoretical active pharmaceutical ingredient weight (binned into volume ranges [e.g. within range of error, low, etc.] or with the calculated value).

Another issue that one reviewer felt was not adequately discussed or described further (in the results or conclusion section) was the discrepancy in the TGA results. For example, according to Appendix C, one of the nicotine samples detected in residuals was found at a different temperature than the positive nicotine control, 3 of the 3 warfarin residuals detected were all found at temperatures different than the positive control, and the one physostigmine sample detected via TGA was different than the pure compound. The reviewers commented that readers are left to figure out what this all means. The warfarin data, for example, are noted by the reviewer to show that as the concentration goes up (from 1 mg to 10 mg), the temperature that the residue peak shows up goes down – this might suggest that purity is inversely related with the mass loss peak. The reviewer noted that this trend seems to be reversed, however, when we consider the pure compound had a much higher Tmax. The reviewer felt that having the authors' comments on the TGA results in the cases where the Tmax was not equal would be helpful, as well as somehow tying that into whether or not the authors think this would change or diminish the observations seen in the mass measurement.
One reviewer commented that the conclusions should also elaborate on the sensitivity of the balance used to measure the drug residual, along with other key study concerns and uncertainties. To identify which results contain potential measurement limitations or concerns, it is necessary to read through the entire report at this point. The summary table proposed above could form the basis of a separate discussion regarding results uncertainty that is currently lacking. An additional column noting any method sensitivity issues or other concerns with the specific result would be prudent. Pulling these individual concerns out will help highlight study limitations and increase transparency in the overall results, thereby leading to better confidence in the overall study results. Results with noted concerns by the authors include Section 5.4.5.2 (method sensitivity issue, limited medication quantity from vendor), Section 5.4.6.2 (method sensitivity issue), Section 5.4.10.1 (inconclusive TGA results), and Section 5.4.10.2 (high standard

deviation). Additionally, only one physostigmine product was obtained for analysis as well – additional discussion in the conclusions or elsewhere should focus on why more of these drug products could not be purchased and how this could affect the overall robustness of the data for one of the three study drugs.

Another reviewer commented that the mass data and TGA data for the blister pack appear to provide a conclusion that there is not an issue with residues in these types of containers. The reviewer felt this to be a really important result that should be elucidated a bit more in the executive summary and conclusions. The nicotine patch data also seem to suggest that residuals are not an issue. However, a reviewer noted the confounding results with the liquid appear to suggest that it would be difficult to make the case that residuals are minor.
10) In summary, reviewers felt the conclusions section of the report could be enhanced greatly by:

1) providing a synthesized review of the study findings that includes a summary table of key findings for all drug-product combinations,
2) highlighting study uncertainties and limitations,
3) noting ways to reduce study uncertainty or limitations if future resources become available, and
4) making a final determination based on the final results in light of study uncertainties and limitations.

Response:

a) The conclusion section was significantly revised (almost re-written) and improved to address all of the above comments and provided a step by step synthesized review of the study findings and a final determination based on these results to answer the research question of the study. The revised conclusion section also presented the limitations of the analysis as well as methods that can be used in future research for the cases where the results of the current techniques were inconclusive. As recommended by the reviewers, Table 6 was created and added to the conclusion section to summarize the study results and the uncertainty and limitations of the analysis. Below id the revised conclusion section in the report:
"*The current study aimed at evaluating if removing the P-listed drugs of warfarin sodium, nicotine, and physostigmine salicylate from their containers is equivalent to triple rinsing the containers. The study was conducted using thermal gravimetric analysis and weight measurements using sensitive balance. The TGA was used to qualitatively evaluate the presence of active pharmaceutical ingredient in the residuals after removing the drug from the rinsed pharmaceutical containers by comparing the* $T_{max\ wt\ loss}$ *of the residuals to that of the pure active pharmaceutical compound. The total amount of residuals in pharmaceutical containers containing warfarin, physostigmine salicylate and nicotine medications after removing the drugs were measured using a sensitive balance. The theoretical "maximum possible weight of residual drug/total residual /container" was calculated for each compound and packaging combination. This calculated result may be used to infer an upper limit for the amount of pharmaceutical*

compound in the total residue remaining in the container. A total of 18 drug/packaging combinations were evaluated in the study. The results obtained in the study are summarized in Table 6 and indicate the following:

- *For the medications in liquid form (Nicotrol nasal spray 10 mg/ml and Physostigmine salicylate 1 mg/ml), there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not triple-rinsed containers contain the active pharmaceutical ingredient. It should be noted that the tested liquid mediations were solutions (not suspensions) and there was no mentioning on the drug package of a requirement or recommendation to shake the medication before use.*
- *For Nicotine inhaler 10 mg/cartridge, there is a difference between triple-rinsed containers and those that are not triple-rinsed. The residues in the not triple-rinsed containers contain the active pharmaceutical ingredient. The amount of nicotine in the residue was not calculated based on experimental results; rather it was calculated based on information provided by the manufacturer. On the package, it was stated that every cartridge contain 10 mg nicotine and only 4 mg out of the 10 mg will be delivered and thus, 6 mg nicotine will be retained in each used cartridge.*
- *For the medications in solid form (i.e., tablet, gum, and lozenge) and patches, the TGA results showed no difference between triple-rinsed containers and those that are not triple-rinsed. However, this conclusion is based on a qualitative analysis by TGA that is limited by the TGA sensitivity. Other analytical techniques (e.g., gas chromatography or liquid chromatography equipped with mass spectrometer) are needed to verify the TGA results for these medications and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any).*

The above conclusions present the straight answer to the main research question of the study which was "Is there a difference between triple-rinsed P-listed pharmaceutical containers and those that are not triple-rinsed?" Additional conclusions are presented below and highlight other findings obtained herein as well as limitations of the analysis:

1. *The medications packaged in blister packs and plastic wraps contained minimal residuals, in the range of the error of the balance used in the study, after removing the drugs. Although the sensitivity of the balance did not allow for determining the actual amount of total residues in these package types, the results infer an upper limit for the total amount of residues in these packages.*
2. *All medications packaged in plastic containers contained measurable amount of residuals (using balance data) after removing the drugs. An exception happened for two medications, Nicorette lozenges 2 mg and Nicorette lozenges 4 mg. Although residues were visually present in the empty containers of these two medications and were detected by TGA, the amount of residues detected by the balance was within the range of the balance error. The balance results in this case were inconclusive.*
3. *The theoretical "maximum possible weight of residual active compound/total residual /container" was calculated for each compound and packaging combination (Table 5).*

The calculated amounts may be used to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container.

4. *Any medication in liquid form must contain the active pharmaceutical ingredient in the residuals. This is because the active pharmaceutical ingredient is homogenously distributed in the liquid. Therefore, for any liquid medication, the actual amount of drug in the residuals can be calculated by knowing 1) the weight of residuals, and 2) the concentration of the active pharmaceutical ingredient in the medication as stated by the manufacturer. Despite this fact, the TGA results for physostigmine medication did not show the presence of the physostigmine compound in the residuals although the calculated amount of physostigmine in the residue in each ampule was 73 µg. The reason for the negative TGA results in this case could be explained by the limited capacity of the cotton piece to absorb all the amount of liquid residue in the empty ampule. This means that only a fraction of the total residue was loaded on the cotton piece and thus, only a fraction of the 73 µg of physostigmine was available to be detected by the TGA. It should be noted that the majority of residue absorbed by the cotton piece was the liquid water solvent as indicated by the $T_{max\ wt\ loss}$ at 103 °C.*
5. *The nicotine nasal spray 10 mg/ml was the only medication to have positive TGA results (active pharmaceutical drug was detected in the residuals) as the residues had a $T_{max\ wt\ loss}$ at 217 ^oC that is representative of nicotine. But the $T_{max\ wt\ loss}$ for the negative control (cotton piece) was shifted in this case which may be attributed to a reaction between the residual liquid and the cotton piece that caused changes in the properties of the cotton piece. Nonetheless, the fact that this medication is in liquid from and contains 67.8 µg of nicotine based on the theoretical calculations suggests that the detected TGA peak at 217 ^oC represent nicotine.*
6. *For the blister packs and nicotine patches, the calculated upper limit for the amount of active pharmaceutical compound in the total residue was relatively low and ranged from 0 to 8 µg. These amounts are upper limit and the actual amounts of active compounds in the residues are more than likely lower because the outer layer of the medication acts as a coating to prevent the loss of the drug until the medication reaches the target location in the body and thus, this layer does not probably contain the drug. The balance and upper limit results support the TGA results which were negative for these pharmaceutical packages.*
7. *For the plastic containers encompassing warfarin tablets (1, 5, and 10 mg), detectable quantities of residues were found in the empty containers. The TGA results for the same containers showed clear peaks for these residues, however, the peaks did not correspond to the warfarin and thus, they most likely represent the coating materials. These data support the aforementioned assumption that the residues in these cases are mainly*

composed of coating materials. Nonetheless, having negative TGA results do not eliminate the possibility of the presence of the active pharmaceutical compound in the residues but if it is present it represent a relatively small fraction.

8. *Conclusions 5, 6, and 7 highlight the importance of considering the balance results and TGA results collectively rather than individually when analyzing the data. "*

***Table 32.** Summary of the results and limitations of analysis*

Medication	Dose	Package Type	TGA Results				Total weight of residues		Calculated Upper Limit for Amount of Active Pharmaceutical Ingredient (µg)
			$T_{max\ wt\ loss}$ for Residues	$T_{max\ wt\ loss}$ for Pure Compound	Results	Limitation of Analysis	Weight (mg)	Limitation of Analysis	
Warfarin	Warfarin sodium tablets, 1 mg	Plastic container	245 °C	313 °C	Negative	Qualitative	19.8	NA	90
	Warfarin sodium tablets, 5 mg	Plastic container	239 °C	313 °C	Negative	Qualitative	17.5	NA	390
	Warfarin sodium tablets, 10 mg	Plastic container	231 °C	313 °C	Negative	Qualitative	19.8	NA	890
	Warfarin sodium tablets, 2 mg	Blister pack	None	313 °C	Negative	Qualitative	0.3	Within range of error	3
	Jantoven tablets, 1 mg	Blister pack	None	313 °C	Negative	Qualitative	0.3	Within range of error	1
	Jantoven tablets, 10 mg	Blister pack	None	313 °C	Negative	Qualitative	0.2	Within range of error	8
Nicotine	Nicorette gum, 2 mg	Blister pack	None	217 °C	Negative	Qualitative	0.3	Within range of error	0.5
	Nicorette gum, 4 mg	Blister pack	None	217 °C	Negative	Qualitative	0.3	Within range of error	0.8
	Nicotine polacrilex gum, 2 mg	Blister pack	None	217 °C	Negative	Qualitative	0.1	Within range of error	0.2
	Nicotine polacrilex gum, 4 mg	Blister pack	None	217 °C	Negative	Qualitative	0.1	Within range of error	0.3

***Table 6.** Summary of the results and limitations of analysis (Cont'd)*

Medication	Dose	Package Type	TGA Results				Total weight of residues		Calculated Upper Limit for Amount of Active Pharmaceutical Ingredient (µg)
			$T_{max\ wt\ loss}$ for Residues	$T_{max\ wt\ loss}$ for Pure Compound	Results	Limitation of Analysis	Weight (mg)	Limitation of Analysis	
Nicotine	Nicorette mini lozenge, 2 mg	Plastic container	306 °C	217 °C	Negative	Qualitative	0.2	Uncertainty of measurement [a]	NA
	Nicorette lozenge, 4 mg	Plastic container	324 °C	217 °C	Negative	Qualitative	0.0	Uncertainty of measurement [a]	NA
	Nicotine transdermal patch, 7 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.1	Within range of error	1.0
	Nicotine transdermal patch, 14 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.0	Within range of error	0.0
	Nicotine transdermal patch, 21 mg	Plastic wrap (peel off)	None	217 °C	Negative	Qualitative	0.0	Within range of error	0.0
	Nicotrol nasal spray, 10 mg/ml	Glass vial	217 °C	217 °C	Positive	Uncertainty with the negative control	67.8	NA	67.8
	Nicotine inhaler, 10 mg/cartridge	Plastic container	NA	NA	NA	Qualitative	NA	NA	6000 [b]
Physostig-mine salicylate	Physostig-mine salicylate, 1 mg/ml	Glass ampule	103 °C	236 °C	Negative	Qualitative	73	NA	73

[a] Although residues were visually present in the empty container and were detected by TGA, the amount of residues detected by the balance was within the range of the balance error. The balance results in this case were inconclusive. [b] This value was not calculated based on experimental results, rather it was calculated based on information provided by the manufacturer. On the package, it was stated that every cartridge contain 10 mg nicotine and only 4 mg out of the 10 mg will be delivered when used.

b) The executive summary was also revised significantly to reflect the updated conclusions and to solve the discrepancies highlighted by the reviewers. Also, information on the study objectives and the experimental test program were included in the revised executive summary because this information was missing in the original version. The new additions and the changes to the executive summary are:

"The primary objective of the current study was to answer the research question "Is there a difference between empty P-listed pharmaceutical containers that are triple-rinsed and those that are not triple-rinsed?" The study objective was accomplished via two tasks: 1) calculating the "maximum possible weight of residual drug/total residual /container" for each compound and packaging combination to infer an upper limit for the amount of active pharmaceutical compound in the total residue remaining in the container and 2) evaluating, qualitatively, the presence of active pharmaceutical ingredient in the residues. The experimental test program included the use of a sensitive balance to determine the total amount of residues in the empty pharmaceutical containers and a thermal gravimetric analysis to qualitatively evaluate the presence of the active pharmaceutical compounds in the residues. The P-listed pharmaceuticals evaluated in the study were nicotine, Coumadin, and physostigmine.

The results of the study indicated the following: 1) all the medications in liquid form (Nicotrol nasal spray 10 mg/ml and Physostigmine salicylate 1 mg/ml) as well as the Nicotine inhaler (10mg/ cartridge) showed a difference between triple-rinsed containers and those that are not triple-rinsed because the residues in the not triple-rinsed ones contained the active pharmaceutical ingredient; 2) the TGA results for the medications in solid form (i.e., tablet, gum, and lozenge) and patches showed no difference between triple-rinsed containers and those that are not triple-rinsed. However, this conclusion is based on a qualitative analysis by TGA that is limited by the TGA sensitivity. Other analytical techniques (e.g., gas chromatography or liquid chromatography equipped with mass spectrometer) are needed to verify the TGA results for these medications and to quantitatively determine the amount of the active pharmaceutical compounds present in the residues (if any); 3) the medications packaged in blister packs and plastic wraps contained minimal residuals, in the range of the error of the balance used in the study, after removing the drugs; 4) medications packaged in plastic containers contained measurable amount of residuals (using balance data) after removing the drugs (except for Nicorette lozenges 2 mg and Nicorette lozenges 4 mg for which the balance data were inconclusive); and 5) a theoretical "maximum possible weight of residual active compound/total residual /container" was calculated and presented for each compound and packaging combination."

c) The reviewers also recommended commenting on the TGA results in the cases where the T_{max} for residues was not equal to that of the positive control. Therefore, the following statement was added for the five cases where the TGA showed peaks for the residues that were different than those of the positive control (sections 5.2.1.1, 5.2.2.1, 5.2.3.1, 5.4.5.1, and 5.4.6.1): "This indicates that the majority of the residues (if not all) represents other chemical compounds that

are used as a capping layer to encapsulate the dose of active pharmaceutical compound within the tablet until the time of use."

d) The reviewers had a comment on why only one physostigmine product was obtained for analysis in the current study. We only tested phsostigmine salicylate injection (1mg/ml) because this is the only form and dose of physostigmine salicylate available in the market.

It should be noted that before we conducted the study, we asked the vendor to generate a list of the forms, doses, and package types for each one of the target medications (nicotine, warfarin and physostigmine). Our request from the vendor was to have a comprehensive list that includes what is available in the market. Once we obtained the list from the vendor, we sent it to the Office of Solid Waste and Emergency Response (OSWER) to seek their feedback on this list and to get their advice on whether more medications need to be added to the list or not. The OSWER consulted with their experts and their response to us was to proceed with the list as is. In summary, the list of medication tested herein was approved by the OSWER as a comprehensive list for the target medications.

Additional Comments

There were some spelling typos (e.g., weigh vs. weight, platic or platsic vs. plastic, Figure 12 when it should be Figure 10, Figure 12 text box is stuck on x-axis) that should be fixed but do not change the accuracy of the results. However, there were some typographical errors that mixed up the drug names for a given section. The drugs listed in Section 5.1.3 and 5.1.4 titles do not match with the drugs listed in the paragraph text. Additionally, Section 5.2.1 notes 1 mg tablets for warfarin in the title, but the medication line states the drug dose is 10 mg. These errors make it more difficult to assume that there is a high level of data quality control regarding the study design and results.

Response:

We do apologize for the mistakes. All the above mentioned mistakes were corrected (please refer to the revised report). Additionally, a revision of the full report was conducted to check and correct other mistakes.

Attachment A: Reviewer Comments as Submitted

Is the Methodology Sufficient to Answer the Research Question Posed?

Shannon Bartelt-Hunt:

- The research question posed by ORD is whether there are differences in pharmaceutical residues between triple rinsed P-listed pharmaceutical containers and untreated containers. To investigate this question, actual P-listed containers were obtained and emptied in a way that simulated actual use. Then, the empty containers were either not treated (not rinsed); single triple rinse with DI water, or a double triple rinse with

methanol to serve as a negative control. The amount of residue in each container was determined using a sensitive balance. The difference in weight between the untreated and treated containers was attributed to any remaining residual. After weighing, the residual was swabbed with a cotton swab and subjected to TGA to qualitatively identify the active pharmaceutical ingredient.

- For tablet or other non-liquid medications, I don't feel that the methodology used was sufficient to answer the research question, which was determining the amount of active pharmaceutical residual in each container. Use of the balance is sufficient to determine the amount of the residual, but there is likely an uneven distribution of the active ingredient in the tablet formulation. The report indicates that the coating or outer layer of the medication likely does not contain the active ingredient. It seems likely that the residual in these containers is predominantly from the coating or outer layer of the medication. It is not clear if the residual remaining in these containers contains the active ingredient or not, as the TGA analysis was inconclusive. No active ingredient was detected in any of the TGA analyses.
- I do think that the methodology of weighing the residual should be sufficient to answer the research question for the case of liquid medicines. In this case, the residual is known to contain the active ingredient, since the active ingredient is homogeneously distributed throughout the medication. Using the manufacturer's information regarding the percentage of the active ingredient, and the amount of residual measured, the amount of pharmaceutically-active residual can be determined. Despite this, it is still troubling that the TGA analysis did not detect any of the active pharmaceutical ingredient in the liquid medications. This may be due to the sensitivity of the TGA analysis, which was not directly discussed.

Jon Powell:

- My understanding is that the research question is "Is there a difference between triple-rinsed P-listed pharmaceutical containers and those that are not triple-rinsed?" A statement of this research question in the executive summary would be helpful and provide necessary context when results are discussed.
- The methodology used was logical: 1. Is there a residue present? 2. Can we qualitatively say what the residue is based on doing TGA on the pure active ingredient then the residue?
- It seems that some type of statistical treatment on the quantitative results could be warranted. I have some slight concerns with the sensitivity of the balance used. A 'readability' of 0.1 mg is important in this study because the differences for some of the

drugs tested were very close to this value – this fact, coupled with a lack of statistical treatment, makes it difficult to conclude that a residue was present.

- Another question of data accuracy relates to some of the reported masses and significant figures – many of the results were reported to several decimal places (e.g., 0.3000 mg on page 25), we are left to wonder how data could be reported that way of the readable limit of the scale was 0.1 mg..

Jennifer Redmond:

- The project objective section of the report states that the primary purpose of the study is to "evaluate if simply removing the drug (specifically nicotine, Coumadin, and physostigmine) from its container is equivalent to triple rinsing the container. It would be useful if the report would state why only these three drugs were chosen for study evaluation (e.g. based on volume usage) and how these drugs relate to other drug types or classes subject to P-listed waste regulations.
- It would be useful if additional detail was presented in the methodological Approach (4.0) section of the report explaining differences in the package types and justifying why the chosen analytical methods were deemed optimal for the given study, potential limitations, and comparison to other considered approaches. The study results suggest that the sensitive balance was not sensitive enough to detect mass balance changes in all packages before and after drug removal, and therefore the drug residue and active pharmaceutical amounts could not be accurately quantified for all drugs, even when active pharmaceutical drug may have been detected in the thermal gravimetric analysis (TGA) results for the same sample.
- Additionally, 4.2 Experimental Steps notes that foil wrap packaging was not tested for plastic wrap peel offs, but does not provide justification for this decision. The study results later suggest that samples with plastic wrap peel contain no residual (within the range of the error of the balance), but the data appear suspect because a portion of the packaging was not tested to confirm that it did not contain drug residual.
- There were some spelling typos (e.g. weigh vs. weight, platic or platsic vs. plastic, Figure 12 when it should be Figure 10, Figure 12 text box is stuck on x-axis) that should be fixed but do not change the accuracy of the results. However, there were some typographical errors that mixed up the drug names for a given section. The drugs listed in Section 5.1.3 and 5.1.4 titles do not match with the drugs listed in the paragraph text. Additionally, Section 5.2.1 notes 1 mg tablets for warfarin in the title, but the medication line states the drug dose is 10 mg. These errors make it more difficult to assume that there is a high level of data quality control regarding the study design and results.

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Are Data Accurate Enough to Answer the Research Question?

Shannon Bartelt-Hunt:

- I believe that the weight data on residual are accurate enough to determine the amount of residual in the container. I do not think that the data are accurate enough to determine the amount of pharmaceutically-active residual. The report doesn't include the minimum level of detection of the active ingredients by TGA. Because no active ingredients were detected using TGA, it is not clear whether no active ingredients were present, or if the TGA was not sensitive enough to detect the small amount of active ingredient in the sample.

Jon Powell:

- The mass results show a downward trend for most of the different containers (non-blister packs) as more rinsing was done, which is expected if there is residue present. So this observation appears to be effective in terms of accuracy to help answer the research question. Please seem my previous comments, though, regarding the reported masses from the Mettler-Toledo scale. Those drugs that showed a mass difference in residuals typically saw differences at the 1 or 10-mg level, so my point about the scale readability may not matter in those cases since the data are pretty clear.
- The QA/QC data appear to suggest that tolerance limits of different instruments were met. Please see my comments below regarding the TGA results.

Jennifer Redmond:

- Overall, the study methods proposed were sound and allowed for the collection and analysis of data regarding:

  1) Whether there is residual contained in the discarded packaging via sensitive balance, and

  2) Whether the residual may contain the active pharmaceutical ingredient via TGA analysis.

- However, there are instances where neither of these methods are sufficient for data evaluation either due to method constraints (e.g. sensitive balance), a need for additional QC (e.g. TGA data), or other uncertainties and study limitations that are not thoroughly discussed in the report at this time. The key concerns associated with the sensitive balance and TGA data are further detailed below.
- Sensitive Balance Data – The sensitive balance was not sensitive enough to detect mass balance changes in all packages before and after drug removal, and therefore the drug

residue and active pharmaceutical amounts could not be accurately quantified for those drugs, even when active pharmaceutical drug may have been detected in the TGA results for the same sample. Additionally, samples with plastic wrap peel were deemed to contain no residual (within the range of the error of the balance), but a portion of the packaging was not tested to confirm that it did not contain drug residual, and these peel offs are lower in mass, and thereby more likely to be constrained by study method limitations given that the smallest readable balance measurement was 0.1 mg. Therefore, certain packaging types may not be suitable for testing with the balance used during the testing. Perhaps a more sensitive balance could at least be secondarily used in cases where either 1) TGA results reveal active pharmaceutical ingredients while the balance does not indicate that there is residuals, or 2) the packaging is constructed of lower weight material (e.g. peel offs).

- TGA Data – A full product listing in the main body of the report and an additional QC of the final number of medications and a summary of TGA failures is needed. In Section 6.3, the authors should not which 4 drug products failed the TGA test to allow for optimal transparency. The reader has to sift through the whole report to find which products fail in the current version of the report. Furthermore, this section notes that 17 medications were tested, but the QAPP and Section 7 Conclusions notes that a different number were tested (18 in conclusions, and 19 in the QAPP).

Do Data Collected Support the Conclusions of the Research?

Shannon Bartelt-Hunt:

- Yes, the data collected in the study do support the conclusion of the report. The report concludes that all medications in plastic containers contained residuals, but that the amount of active pharmaceutical ingredients in the residual could not be determined. I agree with the reports conclusions regarding the liquid drugs, as the active ingredient should be homogeneously distributed throughout the medication.
- Despite this, the results do not sufficiently answer the research question, which was to determine the difference in the amount of pharmaceutically-active ingredient in the rinsed and non-rinsed containers. This could not be answered, because the amount of pharmaceutically-active ingredient (or even the presence of the active ingredient) could not be determined using the methods employed.

Jon Powell:

- As stated in my comment above, and in my comments in the conclusion section of the PDF, the paper would benefit from having some more direct discussion about the results and observations and what the data means.

- One issue that was not discussed or described further (in the results or conclusion section) was the discrepancy in the TGA results – by my count (Appendix C), one of the nicotine samples that was detected in residuals was found at a different temperature than the positive nicotine control, 3 of the 3 warfarin residuals detected were all found at temperatures different than the positive control, and the one physostigmine sample detected via TGA was different than the pure compound. As a reader, we are left to figure out what this all means. Looking at the warfarin data, it appears that as the concentration goes up (from 1 mg to 10 mg), the temperature that the residue peak shows up goes down – this might suggest that purity is inversely related with the mass loss peak. This trend seems to be reversed, however, when we consider the pure compound had a much higher Tmax. In any case, commenting on the TGA results in the cases where the Tmax was not equal would be helpful and somehow tying that into whether or not the authors think this changes or diminishes the observations seen in the mass measurement would be a good addition to the conclusion.
- The mass data and TGA data for the blister pack appear to provide a conclusion that we do not have the issue with residues in these types of containers, which is a really important result that should be elucidated a bit more in the executive summary and conclusion.
- The nicotine patch data also seem to suggest that residuals are not an issue.
- The confounding results with the liquid appear to suggest that it would be difficult to make the case that residuals are minor.

Jennifer Redmond:

- The executive summary of the report notes that the qualitative TGA results show that there is "no observable difference [in the presence of active ingredients] between containers that were triple rinsed and containers that were not" except for nicotine nasal spray. However, the conclusions (Section 7) note that all medications in plastic containers contain measurable residual levels, but it was not possible to determine the amount of active pharmaceutical ingredients using TGA. Furthermore, the conclusions section does not discuss the nasal spray results at all. A step-wise summary of the report findings is necessary to come to a final conclusion on whether or not there is a difference between triple rinsing for some pharmaceutical-package combinations.
- The individual package type or drug results are not summarized in a consistent and thorough manner. Adding a summary table would be a very useful way to review the drug, dose, product, and package types evaluated along with at least qualitative information on whether the TGA results were positive (indicating active drug residual was present in discarded packaging), along with the measured residual weight (binned

into weight ranges, or with the average value), and the theoretical active pharmaceutical ingredient weight (binned into volume ranges [e.g. within range of error, low, etc.] or with the calculated value).

- The conclusions should also elaborate on the sensitivity of the balance used to measure the drug residual, along with other key study concerns and uncertainties. To identify which results contain potential measurement limitations or concerns, it is necessary to read through the entire report at this point. The summary table proposed above could form the basis of a separate discussion regarding results uncertainty that is currently lacking. An additional column noting if there are method sensitivity issues or other concerns with the specific result would be prudent. Pulling these individual concerns out will help highlight study limitations and increase transparency in the overall results, thereby leading to better confidence in the overall study results. Results with noted concerns by the authors include Section 5.4.5.2 (method sensitivity issue, limited medication quantity from vendor), Section 5.4.6.2 (method sensitivity issue), Section 5.4.10.1 (inconclusive TGA results), and Section 5.4.10.2 (high standard deviation). Additionally, only one physostigmine product was obtained for analysis as well – additional discussion in the conclusions or elsewhere should focus on why more of these drug products could not be purchased and how this could affect the overall robustness of the data for one of the three study drugs.
- In summary, the conclusions section of the report could be enhanced greatly by 1) providing a synthesized review of the study findings that includes a summary table of key findings for all drug-product combinations, 2) highlighting study uncertainties and limitations, 3) noting ways to reduce study uncertainty or limitations if future resources become available, and 4) making a final determination based on the final results in light of study uncertainties and limitations.

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